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Respiratory Action of the Intercostal Muscles

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De Troyer, André, Peter A. Kirkwood, and Theodore A. Wilson. Respiratory Action of the Intercostal Muscles. *Physiol Rev* 85: 717–756, 2005; doi:10.1152/physrev.00007.2004.—The mechanical advantages of the external and internal intercostals depend partly on the orientation of the muscle but mostly on interspace number and the position of the muscle within each interspace. Thus the external intercostals in the dorsal portion of the rostral interspaces have a large inspiratory mechanical advantage, but this advantage decreases ventrally and caudally such that in the ventral portion of the caudal interspaces, it is reversed into an expiratory mechanical advantage. The internal interosseous intercostals in the caudal interspaces also have a large expiratory mechanical advantage, but this advantage decreases cranially and, for the upper interspaces, ventrally as well. The intercartilaginous portion of the internal intercostals (the so-called parasternal intercostals), therefore, has an inspiratory mechanical advantage, whereas the triangularis sterni has a large expiratory mechanical advantage. These rostrocaudal gradients result

from the nonuniform coupling between rib displacement and lung expansion, and the dorsoventral gradients result from the three-dimensional configuration of the rib cage. Such topographic differences in mechanical advantage imply that the functions of the muscles during breathing are largely determined by the topographic distributions of neural drive. The distributions of inspiratory and expiratory activity among the muscles are strikingly similar to the distributions of inspiratory and expiratory mechanical advantages, respectively. As a result, the external intercostals and the parasternal intercostals have an inspiratory function during breathing, whereas the internal interosseous intercostals and the triangularis sterni have an expiratory function.

I. INTRODUCTION

Expansion of the rib cage and abdominal wall are prominent features of the inspiratory phase of the breathing cycle. The expansion of the abdominal wall is produced by the action of the diaphragm. Thus, as the diaphragm is activated, its muscle fibers shorten and its dome (which corresponds essentially to the central tendon) moves in the caudal direction, pushing the abdominal viscera caudally and displacing the abdominal wall outward. When the diaphragm in anesthetized dogs, rabbits, cats, and horses is activated selectively by electrical stimulation of the phrenic nerves, however, the tension it exerts at the points of attachment on the lower ribs and the rise in abdominal pressure commonly cause expansion of the most caudal portion of the rib cage, but the fall in pleural pressure causes contraction of a large fraction of the rib cage (23, 69, 108, 183). Measurements of thoracoabdominal motion during phrenic nerve pacing in humans with traumatic transection of the upper cervical cord (24, 196) and during spontaneous breathing in subjects with traumatic transection of the lower cervical cord (76, 163, 200) have shown that the human diaphragm acting alone similarly produces an expansion of the caudal portion of the rib cage but an inward displacement of the cranial half of the rib cage. Therefore, the normal expansion of the rib cage during inspiration must be primarily produced by the intercostal muscles, although in humans the scalenes may also be involved (31, 38, 76, 85, 174). However, the intercostal muscles are diverse and widely distributed throughout the rib cage, and until recently, the respiratory functions of the individual muscles have been poorly understood.

A. Anatomy of Intercostal Muscles

The intercostal muscles form two thin layers that span each of the intercostal spaces. The outer layer, the external intercostals, extends from the tubercles of the ribs dorsally to the costochondral junctions ventrally. The fibers of this layer are oriented obliquely, in the caudal-ventral direction, from the rib above to the rib below. In contrast, the inner layer, the internal intercostals, extends from the sternocostal junctions to near the tubercles of the ribs, and its fibers run in the caudal-dorsal direction from the rib above to the rib below. Thus the intercostal spaces contain two layers of intercostal muscle in their lateral portion but a single layer in their ventral and sometimes in their dorsal portions. Dorsally, in the immediate vicinity of the vertebrae, there may be a small space without internal intercostal muscle fibers. The external intercostal muscle in this area, however, is duplicated in each interspace by the levator costae, a thin, triangular-shaped muscle that originates from the tip of the transverse process of the vertebra and fans out laterally to insert onto the caudal rib. Ventrally, between the sternum and the chondrocostal junctions, the external intercostals are replaced by a fibrous aponeurosis, the anterior intercostal membrane, and the only muscle fibers are those of the internal intercostals. This portion of the internal intercostals is distinguished from the interosseous portion by both its location and its function (see below) and is conventionally called the "parasternal intercostals."

Although the external intercostal muscle does not extend to the ventral region of the rib cage, the parasternal intercostals are covered on their inner surface by a thin muscle called the triangularis sterni or transversus thoracis. This muscle is not usually considered among the intercostal muscles, yet its fibers run cranially and laterally from the dorsal aspect of the caudal half of the sternum to the inner surface of the costal cartilages of the third to seventh ribs. These fibers, therefore, are oriented nearly perpendicular to those of the parasternal intercostals and parallel to the external intercostals.

All the intercostal muscles in a given interspace are innervated by the corresponding intercostal nerve, and although there may be differences in detail among species, the general pattern of innervation is fairly constant. From its origin in the thoracic segment of the spinal cord, the intercostal nerve runs ventrally, between the pleura and the caudal aspect of the rib making up the rostral border of the interspace, and it sends many fine nerve branches (or filaments) (188) along its course to supply the entire internal intercostal muscle, including the parasternal intercostal, the triangularis sterni, and several abdominal muscles. The main nerve trunk, therefore, is commonly called the "internal intercostal nerve" (188). However, this nerve trunk also sends two large branches along its course. In the dorsal portion of the interspace, near the rib angle, the nerve sends a first large branch that perforates the internal intercostal muscle and then runs ventrally between the external and internal intercostal

muscles. This large branch innervates, through a number of fine filaments, the external intercostal muscle and is usually referred to as the "external intercostal nerve" (188). The second large branch perforates both the internal and external intercostal muscles about halfway between the rib angle and the costochondral junction and innervates the external oblique muscle of the abdomen; this branch and the internal intercostal nerve also have cutaneous components.

B. Kinematics of the Ribs

The mechanical action of any skeletal muscle is essentially determined by the anatomy of the muscle and by the structures it displaces when it contracts. The intercostal muscles are morphologically and functionally skeletal muscles, and the primary effect of their contraction is to displace the ribs and thereby to alter the configuration of the rib cage. An understanding of the actions of the intercostal muscles, therefore, requires a clear understanding of the mechanics of the ribs and the rib cage.

Each rib articulates at its head with the bodies of its own vertebra and of the vertebra above, and at its tubercle with the transverse process of its own vertebra. The head of the rib is closely connected to the vertebral bodies by radiate and intra-articular ligaments, such that only slight gliding movements of the articular surfaces can occur. Also, the neck and tubercle of the rib are bound to the transverse process of the vertebra by short ligaments that limit the movements of the costotransverse joint to slight cranial and caudal gliding. As a result, the costovertebral and costotransverse joints together form a hinge, and the respiratory displacements of the rib occur primarily through a rotation around the long axis of its neck, as shown in Figure 1*A* (111, 112, 144, 210). This axis is oriented laterally, dorsally, and caudally. In addition, the ribs are curved and slope caudally and ventrally from their costotransverse articulations, such that their ventral ends and the costal cartilages are more caudal than their dorsal ends (Fig. 1, *B* and *C*). When the ribs are displaced in the cranial direction, therefore, their ventral ends move laterally and ventrally as well as cranially, the cartilages rotate cranially around the chondrosternal junctions, and the sternum is displaced ventrally. Consequently, both the lateral and dorsoventral diameters of the rib cage usually increase (Fig. 1, *B* and *C*). Conversely, a caudal displacement of the ribs is usually associated with a decrease in rib cage diameters. This implies that the muscles that elevate the ribs have an inspiratory effect on the rib cage, whereas the muscles that lower the ribs have an expiratory effect on the rib cage.

C. Historical Perspective

The respiratory functions of the intercostal muscles have been controversial throughout medical history. The archival literature on the subject, in fact, extends back to Galen (~130–200 A.C.) who states that the "outer set effects breathing out, the inner breathing in" (83); in other words, the external intercostals have an expiratory action, and the internal intercostals have an inspiratory action. In the Renaissance period, however, Leonardo da

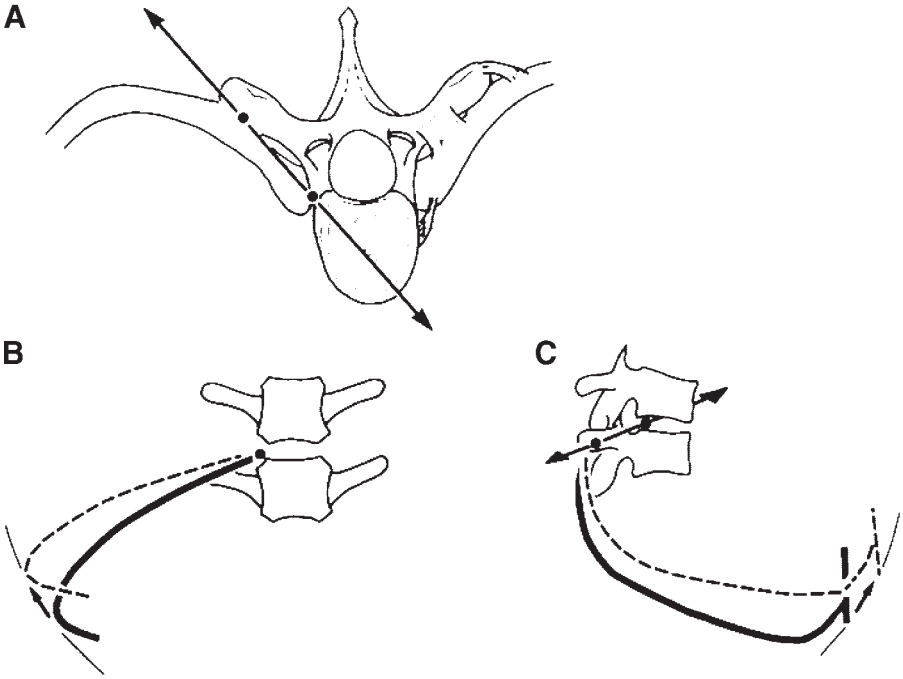

FIG. 1. Respiratory displacements of the rib cage. *A*: diagram of a typical thoracic vertebra and a pair of ribs (viewed from above). Each rib articulates with both the body and the transverse process of the vertebra (closed circles) and is bound to it by strong ligaments (*right*). The motion of the rib, therefore, occurs primarily through a rotation around the axis defined by these articulations (solid line and double arrowhead). From these articulations, however, the rib slopes caudally and ventrally (*B* and *C*). As a result, when it becomes more horizontal in inspiration (dotted line), it causes an increase in both the lateral (*B*) and the dorsoventral (*C*) diameter of the rib cage (small arrows). (From De Troyer A. Respiratory muscle function. In: *Textbook of Critical Care*, edited by W. C. Shoemaker, S. M. Ayres, A. Grenvik, and P. R. Holbrook. Philadelphia, PA: Saunders, 2000, p. 1172–1184.)

Vinci (1452–1519) came to the opposite conclusion (160). Leonardo produced a number of drawings related to the anatomy and the physiology of the respiratory system, and one of them shows a lateral view of the thorax with the ribs and intercostal muscles exposed (Fig. 2, Ref. 112a). The text associated with this drawing states that the fibers interposed between the ribs along the obliquity of the internal intercostals serve to expel the inspired air and that the fibers on the outer side of the ribs in an obliquity contrary to the internal intercostals serve to dilate the ribs and open the lung to take in new air. These thoughts, however, remained largely unknown and had little influence on subsequent opinion. Indeed, Vesalius (1514–1564) stated a little later that both the external intercostals and the internal intercostals are expiratory muscles (202), whereas Borelli (1608–1679) maintained that both are inspiratory muscles (10).

The question remained unsettled. In the middle of the 18th century, it was the subject of a lively controversy between Haller (1708–1777) and Hamberger (1697–1755). Haller (93) claimed, in agreement with Borelli, that both the external intercostals and the internal intercostals are inspiratory muscles, whereas Hamberger (94) argued that the external intercostals are inspiratory muscles and the internal intercostals are expiratory muscles, with the exception of the intercartilaginous portion which is inspiratory. All the theories from Galen to Haller lack solid experimental evidence, so they will not be examined in detail here. The theory of Hamberger, however, deserves a special mention because it provides the basis for the conventional current concept of intercostal muscle action.

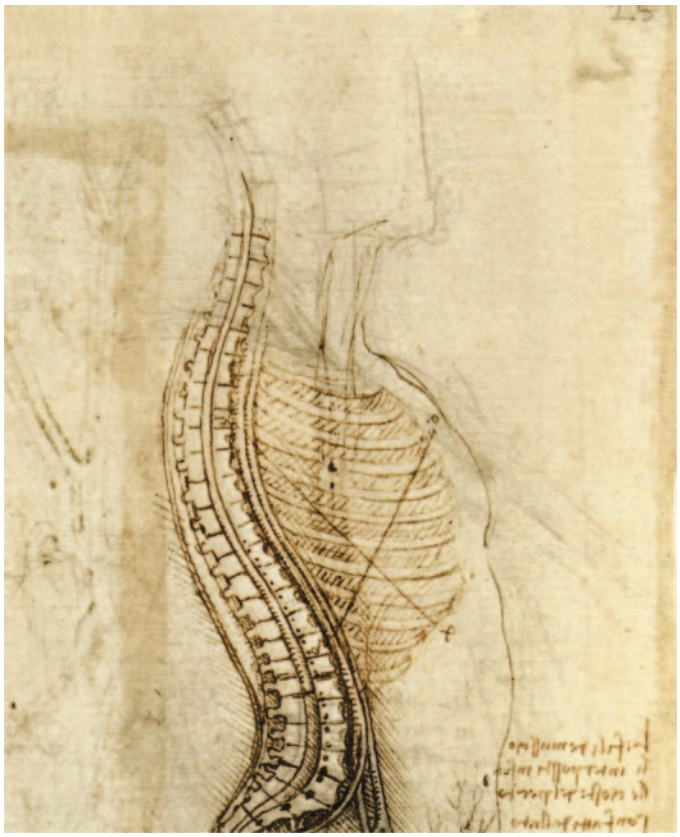

FIG. 2. Reproduction of a drawing by Leonardo da Vinci showing the ribs and the exposed internal intercostal muscles. In the drawing, lines are shown that lie parallel to the directions of the external and internal intercostal muscle bundles, and the notes on the right state that the internal intercostals expel air from the lungs and that the external intercostals dilate the rib cage and open the lungs to take in new air. [From Keele and Pedretti (112a), with permission from Harcourt, Inc.]

This theory is based on an analysis of the model of the ribs and intercostal muscles shown in Figure 3. When an intercostal muscle contracts in one interspace, it pulls the upper rib down and the lower rib up. However, because the fibers of the external intercostal slope caudad and ventrally from the rib above to the rib below, their lower insertion is further from the center of rotation of the ribs (i.e., the costovertebral articulations) than their upper insertion. Consequently, when these fibers contract, exerting equal and opposite forces at the two insertions, the torque acting on the lower rib, which tends to raise it, is greater than that acting on the upper rib, which tends to lower it. The net effect of the external intercostal, therefore, would be to raise the ribs and, with it, to inflate the lung. On the other hand, the fibers of the internal intercostal slope caudad and dorsally from the rib above to the rib below, such that their lower insertion is less distant from the center of rotation of the ribs than their upper insertion. As a result, the torque acting on the lower rib is smaller than that acting on the upper rib, so the net effect of the muscle would be to lower the ribs and to deflate the lung. Hamberger (94) also concluded that the action of the parasternal intercostals should be referred to the sternum, rather than the spine. Therefore, even though these muscles are part of the internal intercostal layer, their contraction should raise the ribs and inflate the lung.

The current widespread acceptance of the theory of Hamberger as a description of intercostal muscle mechanics is probably the result of two factors. First, the rib cage is a complex, three-dimensional structure, and the theory provides a simplified, convenient, two-dimensional, conceptual model for this structure. Second, most electrical recordings from intercostal muscles and nerves in animals appear to be consistent with the conclusions of the theory. It must be appreciated, however, that this theory was not verified experimentally. Also, it was heavily criticized in the middle of the 19th century by Beau and Maissiat (6) and Duchenne (69). The opinions of these physiologists, however, were opposite again. Specifically, Beau and Maissiat (6) stated that both intercostal muscle layers are expiratory, whereas Duchenne (69), based on his observations of rib motion during electrical stimulation of the muscles in a single interspace, maintained that both muscle layers are inspiratory. Both investigators,

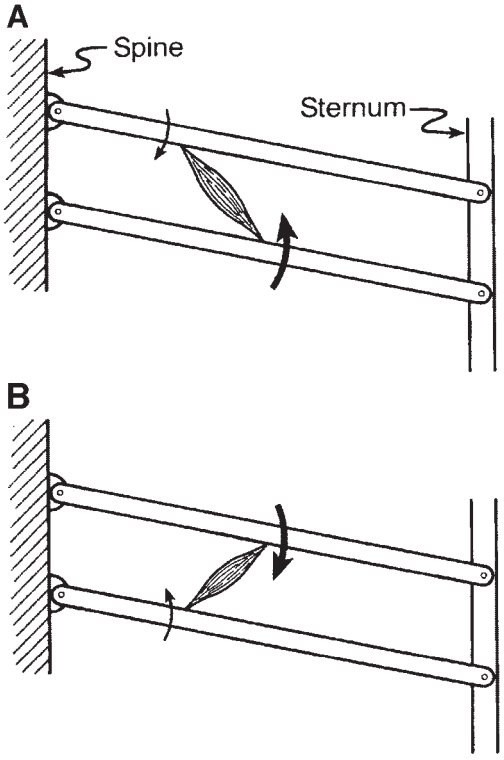

FIG. 3. Diagram illustrating the actions of the intercostal muscles as proposed by Hamberger (94). The two bars oriented obliquely in each panel represent two adjacent ribs. The external and internal (interosseous) intercostal muscles are depicted as single bundles, and the torques acting on the ribs during contraction of these muscles are represented by arrows. When the external intercostal contracts (*A*), the torque acting on the lower rib is greater than that acting on the upper rib; the opposite is true when the internal intercostal contracts (*B*).

however, inferred that the triangularis sterni is expiratory and the levator costae are inspiratory. Finally, it should be noted that throughout history, a number of physiologists have maintained that the intercostal muscles simply stiffen the intercostal spaces and play little or no role in producing the respiratory movements of the ribs.

In the last 15 years, studies have been performed, first in dogs and then in humans, that have led to significant progress in the assessment and understanding of the respiratory actions of the intercostal muscles. This review summarizes these recent developments. One of the most intriguing aspects of these has been the observation of a remarkable relationship between the spatial distribution of neural drive to the intercostal muscles and the spatial distribution of mechanical advantage. This review, therefore, also discusses the possible mechanisms for the distribution of neural drive to the muscles and the possible teleological reasons for such a relationship. The review finally examines the mechanical interactions among the different sets of intercostal muscles and between these muscles and the other muscles involved in the act of breathing, in particular the diaphragm and the abdominal muscles. The nonrespiratory functions of the intercostal muscles, however, in particular their roles in posture maintenance (145), trunk rotation (176, 203), coughing, and vomiting (107, 129, 148, 157), are not covered.

II. RESPIRATORY EFFECTS OF INTERCOSTAL MUSCLES

A. The Maxwell Reciprocity Theorem and Its Application to the Respiratory System

Many intercostal muscles are inaccessible and cannot be activated in isolation. The respiratory effects of these muscles, therefore, have been assessed in recent years by using an indirect method. This method is based on the reciprocity theorem of Maxwell (147). This standard theorem of mechanics applies to any linear elastic system and states that in such a system, the displacement of one point, per unit force applied at a second point, equals the displacement of the second point, per unit force applied to the first point. When applied to the chest wall, this theorem therefore states that the change in lung volume per unit force applied by a muscle is related to the change in length of the muscle when the relaxed chest wall is passively inflated by applying a pressure at the airway opening (206, 207). This relationship can be put in the following form where ΔP_{ao} denotes the change in airway opening pressure produced by muscle contraction with the airway occluded, m denotes muscle mass, σ denotes the active muscle tension per unit cross-sectional area, and $\Delta L/L$ denotes the fractional change in muscle length per unit volume increase of the relaxed chest wall $(\Delta V_L)_{Rel}$

$$\Delta P_{ao} = m\sigma[\Delta L/(L\Delta V_L)]_{Rel} \quad (1)$$

For a machine, such as a lever, *mechanical advantage* is defined as the ratio of the force delivered at the load to the force applied at the handle. By analogy, the mechanical advantage of a respiratory muscle may therefore be defined as $\Delta P_{ao}/m\sigma$ and, according to *Equation 1*, could be evaluated by measuring $[\Delta L/(L\Delta V_L)]_{Rel}$. In other words, a muscle that shortens during passive inflation (negative $\Delta L/L$) would have an inspiratory mechanical advantage and would cause a fall in P_{ao} when it contracts alone. Conversely, a muscle that lengthens during passive inflation (positive $\Delta L/L$) would have an expiratory mechanical advantage and would cause a rise in P_{ao} during isolated contraction. Also, in this review, the *respiratory effect* of a muscle is defined as the value of ΔP_{ao} that is produced by the muscle during a maximal, isolated contraction at its optimal force-producing length (L_o).

The validity of *Equation 1* as a predictor of respiratory effect was initially tested on the canine parasternal

intercostal muscles (54). The animals were anesthetized, placed in the supine posture, and made apneic by mechanical hyperventilation, and the fractional changes in length of the muscle bundles situated near the sternum in the third, fifth, and seventh interspaces were measured during passive inflation of the respiratory system. Next, the internal intercostal nerves in the three interspaces were exposed at the chondrocostal junctions on both sides of the sternum, and with the animal still apneic, the endotracheal tube was occluded. Stimuli of supramaximal voltage were then delivered to the nerves, and the ΔP_{ao} generated by the sternal portion of each parasternal intercostal was measured. The muscle in each interspace was finally harvested, and its mass was measured.

The results of this experiment are shown in Figure 4. With passive inflation, the parasternal intercostal muscle bundles near the sternum shortened in all interspaces, but the fractional muscle shortening decreased from the third to the fifth interspace and decreased further to the seventh interspace. Also, during isolated stimulation, the muscles in all interspaces caused a fall in P_{ao}, thus confirming that they have an inspiratory effect. Moreover, ΔP_{ao}/m was consistently greater for the third interspace than for the fifth, and the latter, in turn, was greater than ΔP_{ao}/m for the seventh interspace. Thus ΔP_{ao}/m for these muscles was proportional to the fractional change in muscle length during passive inflation. In addition, the slope of the relationship between ΔP_{ao}/m and the change in muscle length during passive inflation should be the maximal active muscle tension per unit cross-sectional area (σ), and in vitro measurements of this variable in a number of limb and respiratory muscles in animals and in humans have yielded values ranging between 2.2 and 3.5 kg/cm^2 (19, 77, 78). As shown in Figure 4, a line with a slope of 3.0 fitted the data on the canine parasternal intercostals well.

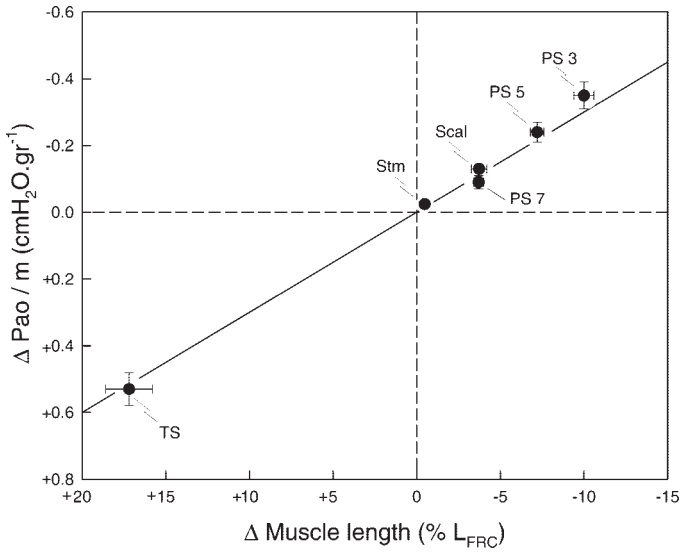

FIG. 4. Relationship between the fractional changes in length of the canine respiratory muscles during a one-liter passive inflation and the changes in airway opening pressure per unit muscle mass (ΔP_{ao}/m) during maximal, isolated muscle contraction. The data shown are the mean ± SE values obtained for the parasternal intercostals (PS) in the third, fifth, and seventh interspaces, the sternomastoids (Stm), the scalenes (Scal), and the triangularis sterni (TS). The fractional changes in muscle length are expressed as percentage changes relative to the muscle length at FRC (L_{FRC}), and ΔP_{ao}/m is expressed as cmH_2O/g. A negative change in muscle length corresponds to a muscle shortening, and a negative ΔP_{ao}/m indicates an inspiratory effect. Note that there is a unique linear relationship between ΔL and ΔP_{ao}/m for all the muscles (solid line); this relationship has a slope of 3.0. [Redrawn from De Troyer and Legrand (51).]

The validity of *Equation 1* was further tested with similar methods on the main inspiratory muscles of the neck, namely, the scalenes and the sternomastoids, and on the triangularis sterni (51, 137). The results of these tests are also shown in Figure 4. The response of the scalenes to both passive inflation and isolated stimulation was similar to that of the parasternal intercostal in the seventh interspace. The sternomastoids, however, remained about constant in length during passive inflation, and isolated maximal stimulation of the muscles produced a very small ΔP_{ao}/m. In contrast, the triangularis sterni in each interspace showed a large fractional lengthening during passive inflation, and its isolated stimulation caused a large ΔP_{ao}/m, in particular when the stimulation was performed after the length of the muscle was brought near L_o by passive inflation. As a result, ΔP_{ao}/m was uniquely related to $[\Delta L/(L\Delta V_L)]_{Rel}$ for all the muscles, and the coefficient of proportionality (σ) between the two was 3.0 kg/cm^2.

The linearity assumption that underlies Maxwell's theorem was also tested by assessing the interactions between various inspiratory muscles on the lung. Indeed, in a linear elastic system, the resultant effect of different forces acting simultaneously is the sum of the effects of the individual forces. Therefore, if the chest wall were reasonably linear and elastic, the effects of active forces in several muscles on P_{ao} should be additive. Legrand et al. (139) have stimulated electrically the parasternal intercostals and the interosseous (both external and internal) intercostal muscles in dogs with the endotracheal tube occluded, first in two interspaces separately and then in the same two interspaces simultaneously. The ΔP_{ao} measured during simultaneous stimulation of the muscles in two interspaces was, within 10%, equal to the sum of the ΔP_{ao} values produced by stimulation of the muscles in each individual interspace. The ΔP_{ao} produced by the simultaneous contraction of the parasternal intercostals in one interspace and either the scalenes or the sternomastoids was also found to be nearly equal to the sum of the ΔP_{ao} values produced by the two sets of muscles individually (139), and similar results were obtained for both the parasternal intercostals and the interosseous intercostals situated on the left and right sides of the sternum (16). Thus, in all these cases, the changes in

intrathoracic pressure generated by the rib cage muscles were essentially additive, and this finding, combined with the results summarized in Figure 4, provides strong support for the idea that the reciprocity theorem of Maxwell is applicable to the respiratory system. Therefore, to assess the respiratory effects of the external and internal interosseous intercostals in dogs, De Troyer et al. (55) measured the masses of the muscles throughout the rib cage and their fractional changes in length during passive inflation, and for each muscle area, they multiplied $\Delta L/L$ by m and by 3.0.

B. Respiratory Effects of Intercostal Muscles in the Dog

1. Mechanical advantage

The fractional changes in length of the canine external intercostal muscles in the dorsal third, middle third, and ventral third of the even-numbered interspaces during passive inflation are shown in Figure 5*A*. With passive inflation, the muscle in the dorsal third of the second interspace shortened markedly; that is, this muscle area has a large inspiratory mechanical advantage. However, this inspiratory mechanical advantage decreases continuously toward the base of the rib cage, such that it is abolished in the 8th interspace and reversed into an expiratory mechanical advantage in the 10th interspace. In addition, the external intercostal in any given interspace has a smaller inspiratory mechanical advantage or a greater expiratory mechanical advantage as one moves from the angle of the ribs toward the costochondral junctions. As a result, the muscles in the ventral third of the sixth interspace and in the middle and ventral thirds of the 8th and 10th interspaces also have an expiratory mechanical advantage (55).

The canine internal intercostal muscle in the dorsal third of any given interspace has an expiratory mechanical advantage, but these muscles also demonstrate prominent dorsoventral and rostrocaudal gradients (Fig. 5*B*). Thus, in a given interspace, the expiratory mechanical advantage decreases progressively from the angle of the ribs to the costochondral junctions. The expiratory mechanical advantage also decreases gradually from the eighth to the second interspace. Consequently, the muscle in the middle and ventral thirds of the second interspace has an inspiratory, rather than expiratory, mechanical advantage (55). For the internal intercostals, in fact, the trend toward a more inspiratory mechanical advantage continues as one moves further toward the sternum (50). As a result, the parasternal intercostal muscle bundles attached to the costochondral junctions have, on average, no mechanical advantage at all, and the muscle bundles in the vicinity of the sternum have an inspiratory mechanical advantage in all interspaces. These medial parasternal bundles, however, retain a definite rostrocaudal gradient (54), such that the inspiratory mechanical advantage is greatest in the second and third interspaces and then declines gradually from the fourth to the eighth interspace (Fig. 5*B*).

The mechanical advantage of the levator costae has not been assessed. To the extent that the muscle fibers originate from the transverse process of the vertebra and insert on the caudal rib, however, it is clear that the

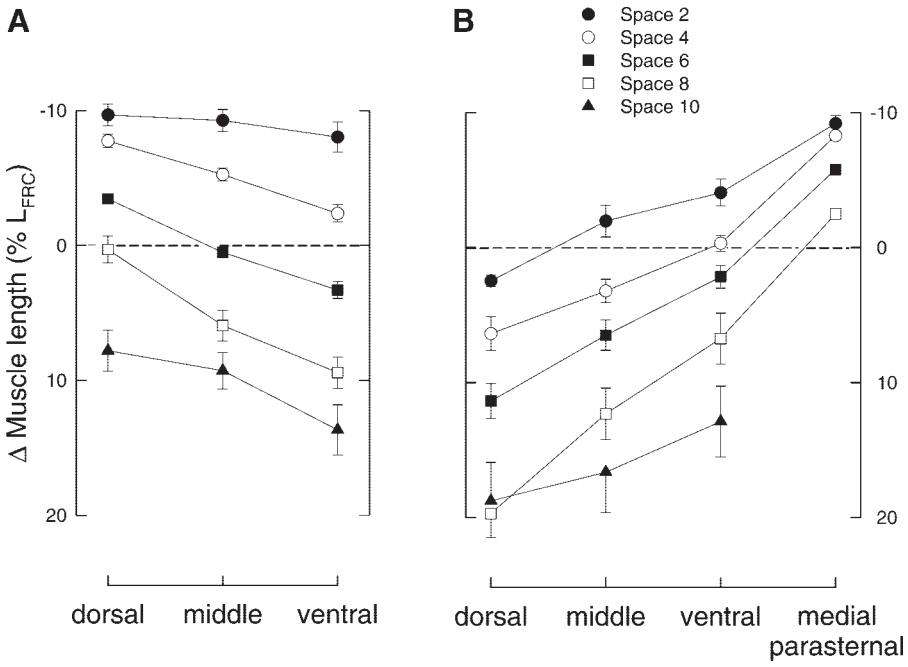

FIG. 5. Mechanical advantages of the canine external (*A*) and internal interosseous (*B*) intercostal muscles in the dorsal third, middle third, and ventral third of the even-numbered interspaces; the mechanical advantages of the medial portion of the parasternal intercostals in interspaces 2, 4, 6, and 8 are also shown. The data are the mean ± SE fractional changes in muscle length during a one-liter passive inflation; negative values indicate inspiratory mechanical advantages, and positive values indicate expiratory mechanical advantages. [Redrawn from De Troyer et al. (55).]

muscle in every interspace has an inspiratory mechanical advantage. As for the external intercostal in the dorsal portion of the rib cage, this inspiratory mechanical advantage would also be expected to decrease gradually with increasing interspace number. In contrast, as pointed out in the previous section, the triangularis sterni has a large expiratory mechanical advantage in all interspaces (51).

2. Muscle mass

In the dog, external intercostal muscle mass is greatest in the dorsal third of the rostral interspaces, and it decreases progressively both toward the base of the rib cage and toward the costochondral junctions (55). Conversely, although the mass of internal interosseous intercostal muscle does not demonstrate any clear-cut dorsoventral gradient, it shows a threefold increase from the rostral to the caudal interspaces. Thus the spatial distributions of external and internal intercostal muscle masses are essentially the same as the spatial distributions of mechanical advantage.

Both muscles, however, are thinner than the parasternal intercostals. In animals with body masses between 15 and 25 kg, the mass of parasternal intercostal muscle in a given interspace (both sides of the sternum) is 10–11 g. In contrast, the mass of external intercostal muscle in a given rostral interspace is only 4–5 g, and the mass of internal interosseous intercostal muscle ranges from 2.5 g in the most rostral interspaces to 7.5 g in the caudal interspaces. As a result, the total mass of parasternal intercostal in interspaces 1–8 is ~75 g, whereas the total masses of external and internal interosseous intercostal in interspaces 1–10 are 45 and 54 g, respectively.

3. Respiratory effect

The respiratory effects computed as described above for the different areas of external and internal intercostal muscle in the dog are shown in Figure 6. These effects have essentially the same distributions as the mechanical advantages, but these are modified by the effect of mass distribution (55). Thus the external intercostals in the dorsal third of the rostral interspaces have an inspiratory effect, whereas those in the middle third and ventral third of the caudal interspaces have an expiratory effect (Fig. 6*A*). Also, the internal interosseous intercostals in the caudal interspaces have an expiratory effect, whereas those in the ventral third of the most rostral interspaces have an inspiratory effect (Fig. 6*B*). However, because the external intercostals in the dorsal third of the rostral interspaces and the internal interosseous intercostals in the caudal interspaces have larger masses, their respective inspiratory and expiratory effects are enhanced. Similarly, the mass of the sternal portion of the parasternal intercostal in a particular rostral interspace is greater than the mass of the external intercostal in the dorsal third of the same interspace by a factor of ~2. Consequently, the former muscle areas have greater inspiratory effects than the latter (Fig. 6*B*).

The levator costae muscle in each interspace must also have an inspiratory effect, but the mass and mechanical advantage of the muscle have not been assessed. This inspiratory effect, therefore, cannot be quantified. In contrast, the triangularis sterni has a clear-cut expiratory effect; its effect in a single interspace is of the same order of magnitude as the inspiratory effect of the sternal por-

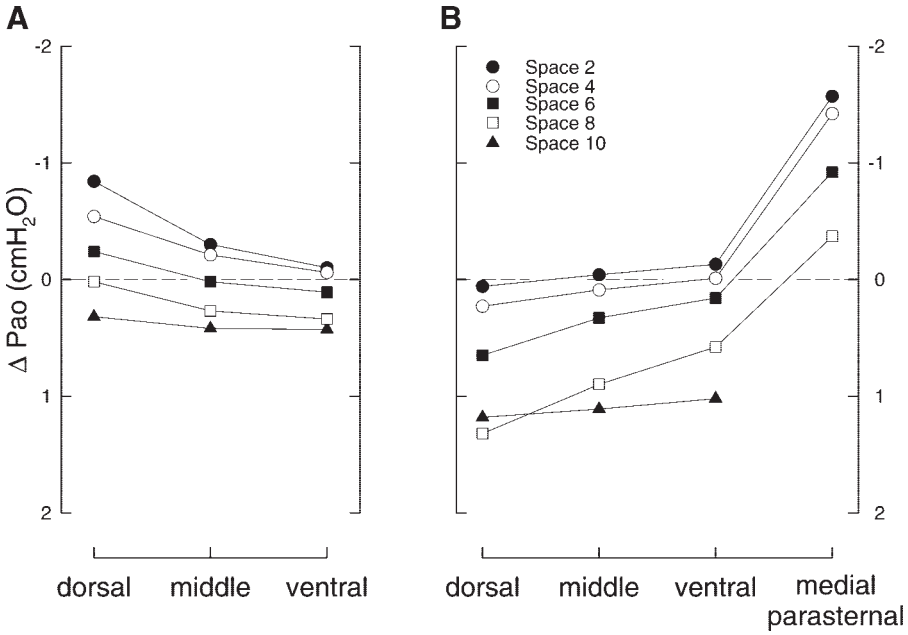

FIG. 6. Respiratory effects of the canine external (*A*) and internal interosseous (*B*) intercostal muscles in the dorsal third, middle third, and ventral third of the even-numbered interspaces; the respiratory effects of the medial portion of the parasternal intercostals in interspaces 2, 4, 6, and 8 are also shown. [Redrawn from De Troyer et al. (55).]

tion of the parasternal intercostal in the second interspace and amounts to 1.75 cmH_2O (51).

We have pointed out in the previous section that the ΔP_{ao} values generated by the canine parasternal or interosseous intercostals in adjacent interspaces are essentially additive. It is most likely, therefore, that the ΔP_{ao} generated by the areas of external or internal interosseous intercostal muscle in the dorsal third, the middle third, and the ventral third of a particular interspace are also additive, and Figure 7 shows the results of such additions for the different even-numbered interspaces; the respiratory effects of the sternal half of the parasternal intercostals are also shown for comparison. The external intercostal in the second interspace has a total inspiratory effect that is similar to the effect of the sternal portion of the parasternal intercostal in the same interspace. However, the inspiratory effect of the external intercostals decreases rapidly from the second to the sixth interspace, and it is reversed into an expiratory effect in the 8th and 10th interspaces. On the other hand, the internal interosseous intercostals in the 8th and 10th interspaces have a large expiratory effect, and although this effect decreases markedly in the cranial direction, it remains expiratory up to the fourth or third interspace. As a result, a maximal contraction of the internal interosseous intercostals in all interspaces would have a definite expiratory effect, whereas a maximal contraction of all the external intercostals would have little or no effect. In contrast, even though the inspiratory effect of the sternal half of the canine parasternal intercostals also decreases from the second interspace to the eighth (Figs. 6 and 7),

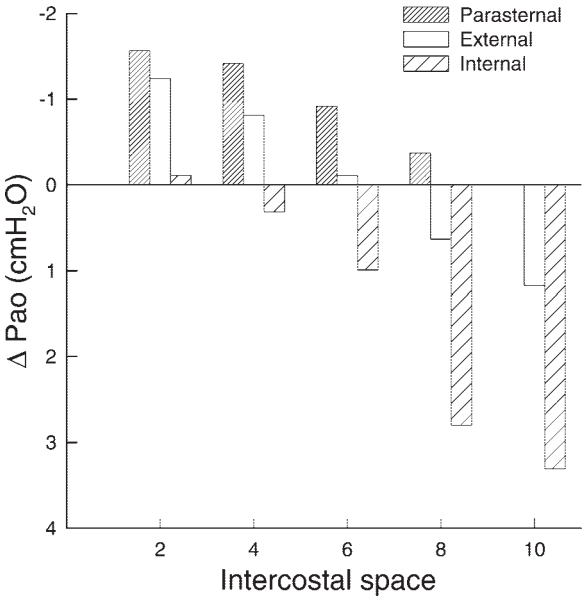

FIG. 7. Net respiratory effects of the canine parasternal intercostal (sternal portion), external intercostal, and internal interosseous intercostal muscles in the even-numbered interspaces. [Redrawn from De Troyer et al. (55).]

a maximal contraction of these muscle bundles in all interspaces would have a clear-cut inspiratory effect.

As described in section II*A*, the ΔP_{ao} values measured experimentally for the parasternal intercostals and the triangularis sterni are very close to the computed values. For the external and internal interosseous intercostals, however, the only data that can be compared with the computed ΔP_{ao} values are those reported by Ninane et al. (169), and these data differ slightly from the computed values. Thus these investigators produced electrical stimulation of the external and internal interosseous intercostals in the third and seventh interspaces in dogs by inserting pairs of copper wires between the two muscle layers from the costochondral junctions to the angles of the ribs; the two intercostal muscles, therefore, were activated simultaneously. When the muscles in the third interspace were activated, pleural pressure (P_{pl}) fell by 0.5–1.9 cmH_2O, and these values agree reasonably well with the computed values. Indeed, if one assumes that the pressure changes produced by the external and internal intercostals in a given interspace are additive, the computed values for the second and fourth interspaces are -1.35 and -0.50 cmH_2O, respectively. On the other hand, when Ninane et al. (169) stimulated the muscles in the seventh interspace, they recorded no change in P_{pl}, whereas the computed ΔP_{ao} values for the sixth and eighth interspaces indicate clear-cut expiratory effects.

This difference may be accounted for, at least in part, by the technique of stimulation used by these investigators (169); that is, because the stimulations were made through wires inserted from the costochondral junctions to the rib angles, they probably involved the levator costae muscle as well. As this muscle has an inspiratory effect, its activation should obscure or at least reduce the expiratory effect of the external and internal interosseous intercostals in the seventh interspace. More importantly, the ΔP_{pl} values reported by Ninane et al. (169) were obtained during stimulation at resting end-expiration (functional residual capacity, FRC). On the other hand, the computed ΔP_{ao} values refer to the pressure changes that the muscles produce during maximal activation at L_o, and the studies of the canine triangularis sterni have clearly illustrated the critical importance of muscle length in determining the ΔP_{ao} generated by expiratory muscles (51). Specifically, when the triangularis sterni in a single interspace was bilaterally stimulated at 1.0 liter above FRC (the muscle then was placed in the vicinity of L_o), ΔP_{ao} averaged $+1.75$ cmH_2O, but when the muscle was stimulated at FRC, ΔP_{ao} was only $+0.80$ cmH_2O. In view of the substantial lengthening of the external and internal interosseous intercostals in the caudal interspaces during passive inflation (Fig. 5), it is most likely that the lung volume corresponding to the L_o of these muscles is also well above FRC. Consequently, their force-generating ability at FRC should be less than maximum. Ninane et al.

(169) did not stimulate the muscles after maximal inflation, yet they reported that the ΔP_{pl} produced by the external and internal interosseous intercostals in the seventh interspace increased from 0 to +0.4 cmH_2O when lung volume was moderately increased above FRC by applying a transrespiratory pressure of +10 to 15 cmH_2O. Irrespective of the probable coactivation of the levator costae, this result fully supports the idea that the intercostal muscles in the caudal interspaces, when activated at appropriate lung volumes, have an expiratory effect on the lung.

C. Mechanisms of the Respiratory Effects in the Dog

As we have pointed out in section I*B*, the theory of Hamberger (94) maintains that as a result of the orientation of the muscle fibers, the external intercostals and the parasternal intercostals have an inspiratory effect and that the internal interosseous intercostals have an expiratory effect. And indeed, in the dog, the external intercostals in the dorsal third of the rostral interspaces and the parasternal intercostals have inspiratory effects, whereas the internal interosseous intercostals over a large fraction of the rib cage have an expiratory effect (Fig. 6). However, the theory of Hamberger cannot explain the dorsoventral and rostrocaudal gradients of respiratory effect for the external and internal interosseous intercostals, and a multiple regression analysis of the data shown in Figure 6 indicates that the orientation of the muscle fibers accounts for only 20% of the total variance of the respiratory effect of these muscles; the position of the muscle fibers along the rib circumference accounts for another 10% of the variance, and interspace number accounts for 55%. In addition, in several areas of the rib cage, the sign of the respiratory effect of the muscles is opposite to that predicted by the theory, thus indicating that other mechanisms play a major role.

A major shortcoming of the theory of Hamberger is that it is based on a two-dimensional model of the rib cage; the ribs in the model are pictured as rigid straight rods and are assumed to rotate around axes that lie perpendicular to the plane of the ribs (Fig. 3). However, as Saumarez (185) and others (55, 208) have pointed out, real ribs are curved, and this curvature has critical effects on the moments exerted by the intercostal muscles, as shown in Figure 8A. The axis of rib rotation is oriented dorsally and laterally, and at point *a* on the rib, the tangent plane of the rib cage is perpendicular to the axis of rotation. For the external intercostal, therefore, the distance between the point of attachment of the muscle on the lower rib and the axis of rib rotation is greater than the distance between the point of attachment of the muscle on the upper rib and the axis of rotation. Consequently, at point *a*, the moment exerted by the muscle on the lower rib is greater than the moment exerted on the upper rib, and the net moment is inspiratory. However, at point *b*, the tangent plane of the rib cage lies parallel to the axis of rib rotation, so the distances between the points of attachment of the muscle on the two ribs and the axes of rib rotation are equal and the net moment exerted by the muscle is zero. Thus the net inspiratory moment of the external intercostal is maximum in the dorsal region of the rib cage, decreases to zero at point *b*, and is reversed to an expiratory moment in the ventral region of the rib cage (Fig. 8*B*). On this basis, the dorsoventral decrease in the inspiratory effect of the external intercostals and the difference between the inspiratory effect of the external intercostals in the dorsal region of the rostral interspaces and the expiratory effect of the triangularis sterni can be understood. Similarly, the net expiratory

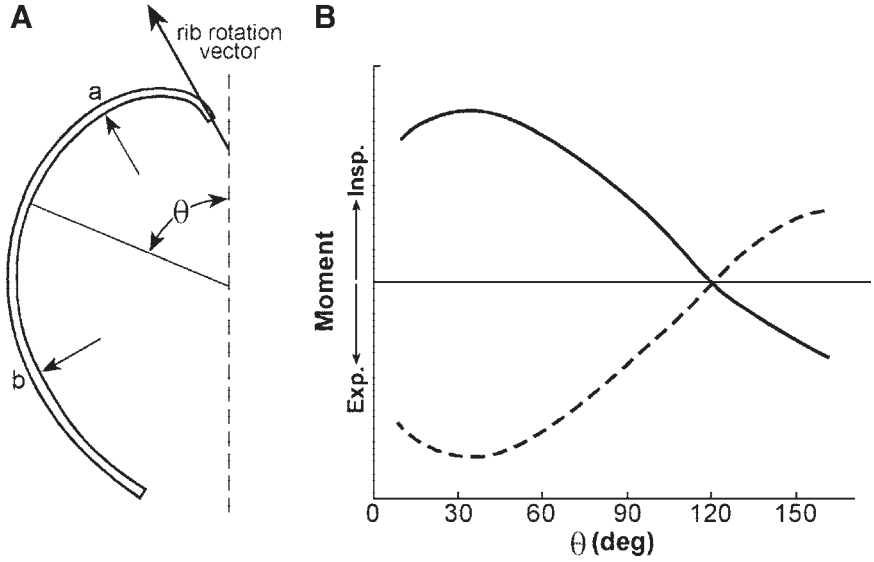

FIG. 8. Effects of rib curvature on the net moment exerted by an intercostal muscle. *A*: plan form of a typical rib in the dog and its axis of rotation (bold vector). At point *a*, the distances between the points of attachment of an intercostal muscle on the lower and upper ribs and the axes of rotation of the ribs are different, and the muscle exerts a net moment on the ribs. At point *b*, however, the distances between the points of attachment of an intercostal muscle on the lower and upper ribs and the axes of rotation of the ribs are equal, and the muscle exerts no net moment. Thus the net moment exerted by the muscle depends on the angular position (θ) around the rib, as shown in *B*. The external intercostal muscle (continuous line) has the greatest inspiratory moment in the dorsal portion of the rib cage (θ between 15 and 60°); this inspiratory moment then decreases as one moves around the rib cage (θ between 60 and 120°) and is reversed into an expiratory moment in the vicinity of the sternum (θ >120°). The internal intercostal muscle (dashed line) shows a similar gradient in expiratory moment.

moment of the internal intercostals is maximum in the dorsal region, decreases in magnitude as one moves away from the spine, and becomes an inspiratory moment in the vicinity of the sternum (Fig. 8*B*). The difference between the expiratory effect of the internal interosseous intercostals in the dorsal region of the rib cage and the inspiratory effect of the parasternal intercostals was already inferred by Hamberger, yet it was not appreciated that the differences between the actions of the muscles in the dorsal and ventral regions are the result of gradual transitions, not abrupt changes of mechanism at the costochondral junctions.

Another shortcoming of the theory of Hamberger is related to the fact that the ribs in the model are linked firmly to each other by the sternum. Such a linkage imposes the constraint that the upper and lower ribs of an interspace have equal compliances. Furthermore, the theory contains the implicit assumption that the coupling between rib displacement and lung volume is the same for the two ribs. Recent studies of the coupling between the ribs and the lung in dogs have demonstrated, however, that the different ribs have different compliances and are coupled differently to the lung (59, 208).

In these studies, external forces were applied in the cranial direction to individual rib pairs in supine, paralyzed animals with the endotracheal tube occluded at FRC. Cranial rib displacement and ΔP_{ao} were measured as the force was increased, and these measurements revealed two important aspects of the mechanics of the rib cage. First, for a given force, rib displacement increased progressively with increasing rib number. Second, the ΔP_{ao} produced by a given rib displacement increased from the 2nd to the 5th rib pair and then decreased markedly from the 5th to the 11th rib pair. As a result, the ratio of ΔP_{ao} to applied force also increased with rib number in the more rostral interspaces and decreased markedly in the caudal interspaces, as shown in Figure 9 (closed circles). Therefore, although the forces exerted by a particular intercostal muscle on the upper and lower ribs are equal in magnitude (and opposite in direction), these forces have different effects on the lung. Specifically, in the rostral half of the rib cage, the fall in P_{ao} produced by the cranial force on a particular rib is larger than the rise in P_{ao} caused by the caudal force on the rib above, so a hypothetical intercostal muscle lying parallel to the longitudinal body axis would have a net inspiratory action on the lung during isolated contraction. On the other hand, in the caudal half of the rib cage, the fall in P_{ao} produced by the cranial force on a particular rib is much smaller than the rise in P_{ao} produced by the caudal force on the rib above, so an intercostal muscle lying parallel to the longitudinal body axis would have a net expiratory effect. In other words, the nonuniform coupling between the ribs and the lung confers an inspiratory bias to both the external and internal interosseous intercostals in the rostral interspaces and an expiratory bias to both muscle groups in the caudal interspaces.

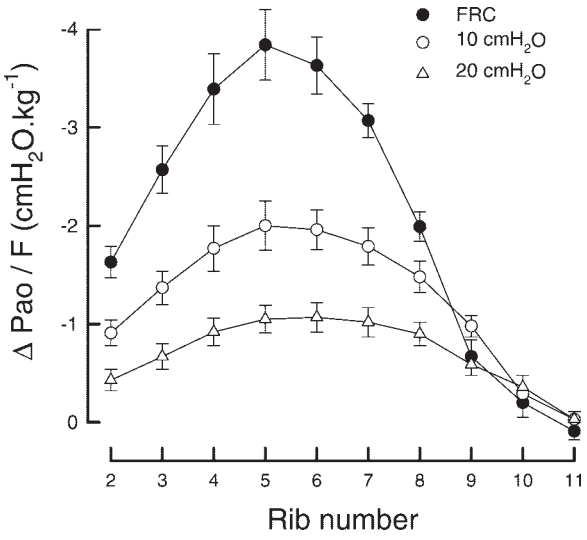

FIG. 9. Coupling between the ribs and the lung in dogs. These data are the mean ± SE values of the changes in airway opening pressure (ΔP_{ao}) per unit force (F) obtained during external loading of individual rib pairs in seven animals. Note that at resting end-expiration (FRC; ●), ΔP_{ao}/F increases from the second to the 5th rib pair and then decreases continuously to the 11th rib pair. Note also that ΔP_{ao}/F for ribs 2–8 decreases markedly when lung volume is increased from FRC to 10 cmH_2O (○) and 20 cmH_2O (△) transrespiratory pressure; in contrast, for ribs 9 and 10, ΔP_{ao}/F increases slightly. [From De Troyer and Leduc (49).]

The nonuniform coupling between the ribs and the lung is probably related to differences between the areas of the lung subtended by the different ribs (59). In the dog, the radii of the ribs in the rostral half of the rib cage increase gradually with increasing rib number (144). In this half of the rib cage, therefore, the area of the lung subtended by a particular rib should be greater than that subtended by the rib above, and hence, the change in P_{ao} induced by a displacement of this particular rib should also be greater. On the other hand, the radii of the ribs in the caudal half of the rib cage also increase with increasing rib number in the dog (144), but these ribs are in part apposed to the abdomen through the diaphragm, rather than the lung (154, 155). At resting end-expiration, the most caudal ribs are even entirely apposed to the abdomen. Consequently, it would be expected that a cranial displacement of these ribs would result primarily in an expansion of the ventral abdominal wall and a fall in abdominal pressure, and that the fall in P_{ao} would be only secondary, due to the (passive) caudal displacement of the diaphragm. Recent measurements of the changes in abdominal pressure during rib loading have confirmed this prediction (49); that is, the fall in P_{ao} observed during loading of the 4th rib pair was greater than the fall in abdominal pressure, whereas during loading of the 10th

rib pair, the fall in P_{ao} was much smaller than the fall in abdominal pressure.

The conclusion thus can be drawn that the respiratory effects of the canine intercostal muscles are the result of two mechanisms (208). The predominant mechanism is the nonuniform coupling between the ribs and the lung and the consequent difference between the respiratory effects of equal and opposite forces on adjacent ribs. This mechanism has a larger effect in the ventral region of the rib cage than in the dorsal region, and it causes the dependence of respiratory effect on interspace number. The second mechanism is the "Hamberger mechanism," modified to account for the three-dimensionality of the rib cage. This mechanism is the result of the difference between the magnitudes of the moments applied to the upper and lower ribs of an interspace, and this difference, in turn, depends on the orientation of the muscle. The magnitude of the effect of this mechanism is larger in the dorsal region of the rib cage than in the ventral region, and its sign is reversed in the vicinity of the costochondral junctions. It is responsible for the difference between the respiratory effects of the external and internal intercostals. Although these two mechanisms operating together account well for the respiratory effects of the external and internal intercostals in most interspaces, it must be stressed that they do not explain the large expiratory effects of the muscles in the most caudal interspaces. At this point, the mechanism for these large expiratory effects is still unclear.

D. Respiratory Effects of Intercostal Muscles in Humans

The intercostal muscles in humans are even less accessible than those in the dog. Their respiratory effects, therefore, were assessed by the following method. The muscles were first dissected in cadavers to measure the orientations of the muscle fibers relative to the ribs and to determine muscle masses (m in *Eq. 1*) (209). Although the cadavers were carefully selected and did not show any evidence of overt undernutrition, they had a 50% reduction in scalene and sternomastoid muscle mass compared with young healthy individuals (138). It was assumed, therefore, that the intercostal muscles in cadavers were similarly atrophied and, hence, the measured values of intercostal muscle mass were multiplied by two. Healthy individuals were then placed in a computed tomographic (CT) scanner to determine the shape of the ribs and their precise transformation during passive inflation, and from these data, the fractional changes in length of lines having the orientations of external and internal interosseous intercostals were computed so as to assess the mechanical advantages of the muscles $\{[\Delta L/(L\Delta V_L)]_{Rel}$ in *Eq. 1*$\}$. The mechanical advantages of the parasternal intercostals and triangularis sterni were similarly computed from values of the orientation of the costal cartilages obtained from CT images (53). The values of mechanical advantage were finally multiplied by the values of muscle mass, measured in cadavers and corrected for muscle atrophy, and by σ (i.e., 3.0 kg/cm^2) to evaluate the respiratory effects of the muscles throughout the rib cage (53, 209).

1. Mechanical advantage

The topographic distribution of mechanical advantage among the external intercostal and parasternal intercostal muscles in humans is qualitatively similar to that in the dog. As in the dog, the human external intercostals in the dorsal portion of the rostral interspaces (and presumably the levator costae) have a clear-cut inspiratory mechanical advantage, and this inspiratory mechanical advantage decreases continuously toward the base of the rib cage and toward the costochondral junctions. As a result, the external intercostals in the ventral portion of interspaces 6–8 have an expiratory mechanical advantage. Also, the parasternal intercostal muscle in every interspace has an inspiratory mechanical advantage, and this advantage decreases gradually from the second to the fifth interspace. It must be pointed out, however, that in humans, the parasternal intercostals do not extend beyond the fifth interspace, and the mechanical advantage of the muscle in that interspace is very small.

As in the dog, the triangularis sterni muscle in humans has an expiratory mechanical advantage in every interspace, and this is particularly strong in the more caudal (5th and 6th) interspaces. The internal interosseous intercostals in humans also have an expiratory mechanical advantage throughout the rib cage. The striking difference observed in the dog between the interosseous and intercartilaginous portions of the internal intercostals is thus maintained in humans. However, the topographic distribution of the expiratory mechanical advantage of the internal interosseous intercostals in humans differs from the dog in two respects. First, the expiratory mechanical advantage of the muscle in the dorsal portion of the rib cage in humans decreases from the top to the base of the rib cage, whereas in the dog, it gradually increases. Second, the expiratory mechanical advantage of the muscle in humans is greatest in the ventral portion, rather than the dorsal portion of the caudal interspaces. These differences are probably the result of the species differences in rib cage shape and rib displacements (see sect. II*E*).

2. Muscle mass

The topographic distribution of external intercostal muscle mass in humans is also qualitatively similar to that observed in the dog. The mass of the muscle is thus greatest in the dorsal half of the rostral in-

terspaces, and from there it decreases gradually in both the caudal and the ventral direction. Consequently, the masses of the external intercostals in the dorsal half and the ventral half of the eighth interspace are only 61 and 35%, respectively, of the muscle mass in the dorsal half of the second interspace. On the other hand, the mass of internal interosseous intercostal muscle in humans does not show any definite rostrocaudal gradient and is slightly larger in the ventral than in the dorsal portion of the rib cage.

The masses of external and internal interosseous intercostal muscle in humans, however, are much larger than the masses of parasternal intercostal and triangularis sterni muscle (53, 209). Thus, after the values of muscle mass measured in the cadavers were corrected for muscle atrophy, the average total mass of external intercostal muscle in interspaces 1–8 was 208 g, and the average total mass of internal interosseous intercostal was 138 g. In contrast, the total masses of the parasternal intercostals and triangularis sterni were only 32 and 18 g, respectively.

3. *Respiratory effect*

The maximum ΔP_{ao} values computed for the areas of external and internal intercostal muscle in the dorsal half and the ventral half of the different even-numbered interspaces in humans are shown in Figure 10. As a result of the distributions of mechanical advantage and muscle mass, the effect of the external intercostals in the dorsal portion of the rostral interspaces is clearly inspiratory (Fig. 10*A*). As in the dog, however, this effect shows definite dorsoventral and rostrocaudal gradients, such that the ΔP_{ao} values for the muscles in the dorsal half of the fourth interspace and the ventral half of the second interspace are only half the value for the muscle in the dorsal half of the second interspace. The computed ΔP_{ao} values for the external intercostals in the dorsal half of the sixth and eighth interspaces are even lower, and in the ventral half of these caudal interspaces, the respiratory effect of the external intercostal is reversed into an expiratory effect. Although the internal interosseous intercostals in humans have an expiratory effect throughout the rib cage, they also demonstrate strong dorsoventral and rostrocaudal gradients (Fig. 10*B*).

The parasternal intercostals in humans have an inspiratory effect in every interspace (Fig. 10*B*), and the triangularis sterni has an expiratory effect. However, whereas the parasternal intercostals in the dog have a greater muscle mass than the external intercostals, in humans the parasternal intercostals are thinner than the external intercostals. If one assumes that, as in the dog, the ΔP_{ao} values generated by the areas of external or internal interosseous intercostal muscle in the dorsal and ventral portions of a particular interspace in humans are additive, the total inspiratory effect of the external intercostal in the second interspace is therefore approximately five times greater than the inspiratory effect of the parasternal intercostal in the same interspace (Fig. 11). Such a difference is also present in the fourth and sixth interspaces, although the inspiratory effects of both muscles in these interspaces are smaller. In contrast, the internal interosseous intercostals have a definite expiratory effect in all interspaces, even though this effect decreases gradually from the eighth to the second interspace (Fig. 11). Because the mass of the internal intercostal muscle in a given interspace is much greater than the mass of the triangularis sterni, the total ΔP_{ao} value computed for the internal intercostal in the sixth interspace, for example, is approximately seven times

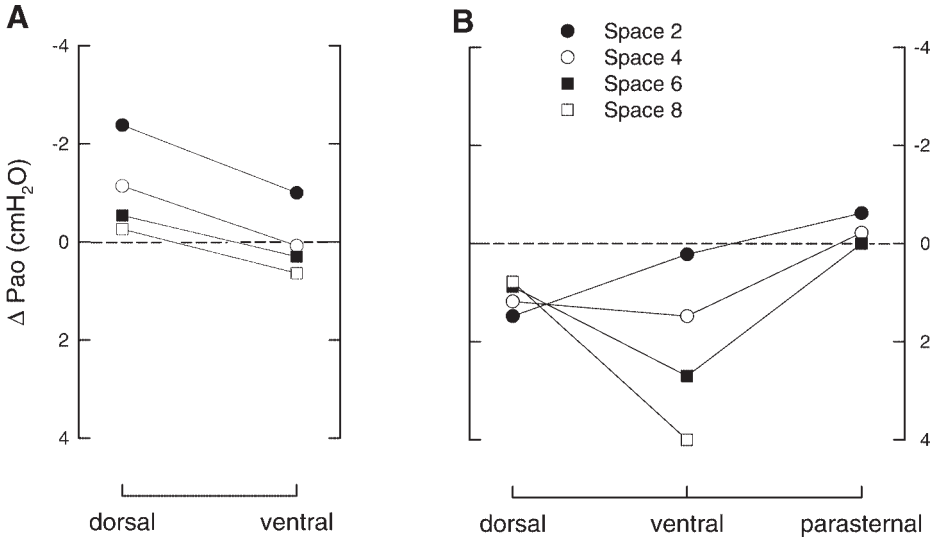

FIG. 10. Computed respiratory effects of the human external (*A*) and internal interosseous (*B*) intercostal muscles in the dorsal half and the ventral half of the even-numbered interspaces. The respiratory effects of the parasternal intercostals in interspaces 2, 4, and 6 are also shown. [Redrawn from Wilson et al. (209).]

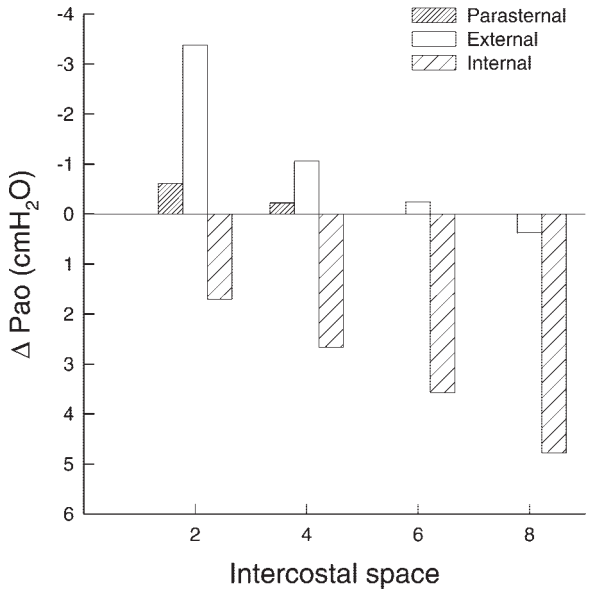

FIG. 11. Net respiratory effects of the parasternal intercostal, external intercostal, and internal interosseous intercostal muscles in the even-numbered interspaces in humans. Note that the values reported for the parasternal intercostals in this figure correspond to the entire muscles and not to their sternal portion alone (as in Fig. 7). [Redrawn from Wilson et al. (209); data for parasternal intercostals from De Troyer et al. (53).]

greater than the computed ΔP_{ao} value for the triangularis sterni in the same interspace.

E. Mechanisms of the Respiratory Effects in Humans

We have emphasized in section II*C* that the respiratory effects of the intercostal muscles in the dog are the result of two mechanisms. The first mechanism is the nonuniform coupling between the ribs and the lung and the consequent difference between the respiratory effects of equal and opposite forces on adjacent ribs. This mechanism has a greater effect in the ventral region of the rib cage than in the dorsal region, and as in the dog, the human intercostals in the ventral region do have an inspiratory bias in the second interspace and an expiratory bias that increases with interspace number in the more caudal interspaces (Fig. 10). Thus, although it has not been possible, as yet, to assess the coupling between the ribs and the lung in humans, the observed distributions of the respiratory effects of the human intercostal muscles suggest that this coupling has a similar pattern to that in the dog. The second mechanism, the "Hamberger mechanism," is the result of the orientation of the muscle fibers and the difference between the moments exerted by these fibers on adjacent ribs. The external and internal intercostal muscles have similar orientations in humans and in the dog. In humans, however, the rib cage at FRC is larger along its lateral than its dorsoventral axis, whereas in the dog, as in most quadrupeds, it is larger along its dorsoventral axis. Consequently, the tangent plane of the rib cage in the dorsal region is close to perpendicular to the axis of rib rotation over a longer portion of the rib circumference in humans than in the dog, so the large inspiratory moment of the external intercostals in the dorsal region and the large expiratory moment of the internal intercostals should be better maintained. In addition, the ribs in humans are slanted caudally more than those in the dog (144, 209). Therefore, the angle between the line of the internal intercostal muscle bundles and the longitudinal body axis is greater, and the difference between the distances from the points of attachment on the lower and upper ribs and the axes of rib rotation is also greater. As a result, the net moment is greater, and this should enhance the expiratory effect of the internal interosseous intercostals in the ventral portion of the caudal interspaces.

F. Implication

In the dog, both the external intercostal muscles and the internal interosseous intercostal muscles have an inspiratory effect in some areas and an expiratory effect in other areas (see sect. II*B*). This implies that the function of these muscles during breathing depends on the topographic distribution of neural drive. For example, if the external intercostals in the dorsal region of the rostral interspaces were active during the inspiratory phase of the breathing cycle, they would inflate the lung. However, if the external intercostals in the ventral region of the caudal interspaces were active during the expiratory phase of the cycle, they would deflate the lung. Similarly, activation of the internal interosseous intercostals in the caudal interspaces during expiration would deflate the lung, but activation of the internal intercostals in the ventral region of the most rostral interspaces during inspiration would contribute to lung inflation. The results described in section II*D* similarly imply that in humans, the external intercostals could have an inspiratory function, an expiratory function, or both, depending on the spatial distribution of neural drive during inspiration and expiration.

III. DISTRIBUTION OF NEURAL DRIVE TO THE INTERCOSTAL MUSCLES DURING BREATHING

A. Distribution of Neural Drive in Quadrupeds

Since the initial studies of Bronk and Ferguson (12), a number of electrical recordings from intercostal mus-

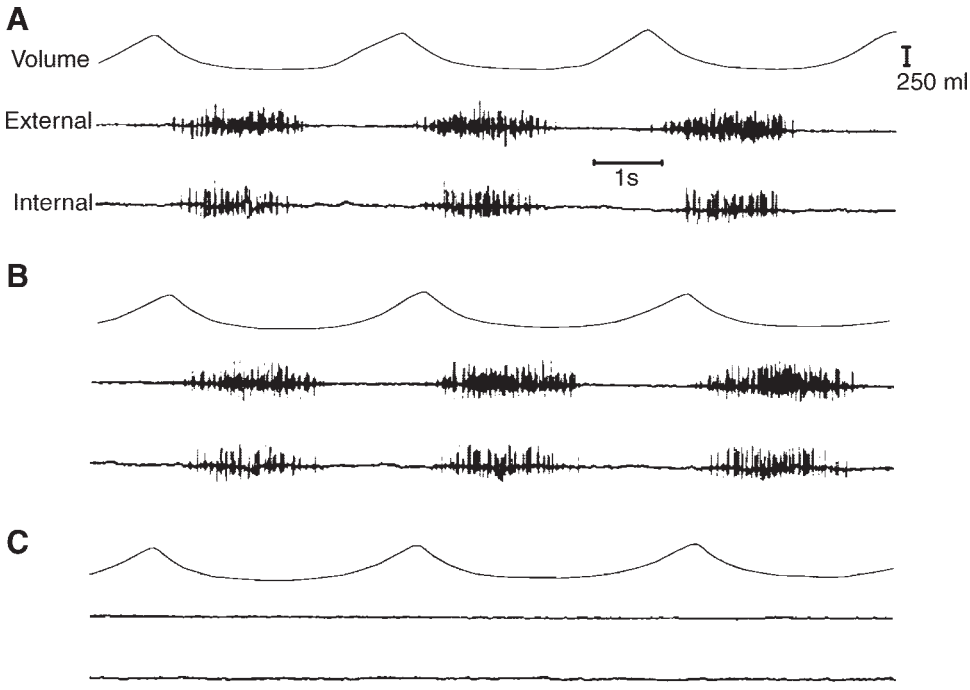

FIG. 12. Traces of EMG activity recorded from the external and internal interosseous intercostal muscles in the ventral third of the eighth interspace in a representative dog during resting breathing in the control condition (*A*), after section of the external intercostal nerve (*B*), and after section of the internal intercostal nerve (*C*). Note the persistence of phasic expiratory activity in the external intercostal muscle after section of the external intercostal nerve. [From Legrand and De Troyer (135).]

cles and nerves in anesthetized cats (5, 92, 100, 124, 127, 188), dogs (32, 41, 46), and baboons (44) have shown that the parasternal intercostals, the external intercostals, and the levator costae are active during inspiration. On the other hand, the triangularis sterni and the internal interosseous intercostals are active during expiration (56, 73, 92, 106, 188, 194). In fact, it has been universally recognized that the parasternal intercostals and the levator costae are active only during inspiration and that the triangularis sterni is active only during expiration. In view of the mechanical advantage of the muscles (Figs. 4 and 5), the conclusion can therefore be drawn that in quadrupeds, the parasternal intercostals and levator costae have an inspiratory function during breathing, and the triangularis sterni has an expiratory function.

However, disparate reports of the activity patterns of the external and internal interosseous intercostals exist in the literature. Earlier studies in dogs by Gesell (87) also reported efferent discharges to the external intercostal muscles in the caudal interspaces during expiration and to the internal interosseous intercostal muscles in the most rostral interspaces during inspiration. Similar observations were made in decerebrate cats by LeBars and Duron (133) and in awake dogs by Carrier (18). Because the canine external intercostals in the caudal interspaces have an expiratory mechanical advantage and the internal interosseous intercostals in the most rostral interspaces have an inspiratory mechanical advantage (Fig. 5), these observations therefore raise the possibility that in the rostral interspaces, both the external and internal interosseous intercostals have inspiratory functions during breathing and that in the caudal interspaces, both have expiratory functions. Alternatively, the external intercostals in the caudal interspaces and the internal intercostals in the rostral interspaces are particularly thin, so the expiratory activity recorded from the former and the inspiratory activity recorded from the latter could simply be the result of cross-contaminations.

To differentiate between these two possibilities, Legrand and De Troyer (135) reexamined with selective denervation procedures the pattern of activity of the canine external intercostal muscles with an expiratory mechanical advantage and the activity of the internal interosseous intercostals with an inspiratory mechanical advantage. In agreement with the observations of Gesell (87), LeBars and Duron (133), and Carrier (18), phasic expiratory discharges were recorded from the external intercostal muscles in the ventrolateral portion of the caudal interspaces (Fig. 12*A*). However, this expiratory activity remained unchanged after section of the external intercostal nerve (Fig. 12*B*), and it disappeared only after section of the internal intercostal nerve in the same interspace and abolition of expiratory activity in the underlying internal intercostal muscle (Fig. 12*C*); that is, the expiratory discharges recorded in the external intercostal muscles in the caudal segments of the rib cage were due to impulses traveling along the internal, rather than the external, intercostal nerves. Discharges were also recorded from the internal interosseous intercostal muscle in the ventral portion of the second interspace during the inspiratory phase, in particular when the inspiratory mechanical load was increased. These discharges, however, were eliminated after denervation of the external intercostal muscles in the same interspace and in the contig-

uous interspaces (135). Thus these studies confirmed the observations in cats by Sears (188), Kirkwood and coworkers (124, 127), and Greer and Martin (92) that the external intercostal muscles, when active, are active only during inspiration and the internal interosseous intercostal muscles, when active, are active only during expiration.

Legrand and De Troyer (135) subsequently evaluated in a quantitative manner the spatial distributions of external intercostal inspiratory activity and internal intercostal expiratory activity. This quantitative assessment was made by normalizing the activity recorded from each muscle area during breathing by the activity recorded during tetanic, supramaximal stimulation of the corresponding external or internal intercostal nerve (maximal activity), and the results obtained during resting breathing and during breathing against increased mechanical loads are shown in Figures 13 and 14. Whether during resting breathing or during breathing against elevated inspiratory airflow resistance, external intercostal inspiratory activity in the dorsal part of the rib cage was greatest in the most rostral interspaces and declined gradually in the caudal direction (Fig. 13*A*); the external intercostal in the dorsal portion of the eighth interspace, in fact, remained almost invariably silent. Furthermore, external intercostal inspiratory activity in a particular rostral interspace decreased consistently from the dorsal to the lateral region and decreased further from the lateral to the ventral region (Fig. 13*B*). Qualitative descriptions of external intercostal inspiratory activity in cats have reported similar rostrocaudal and dorsoventral gradients (5, 92, 124, 127), and this leads to the conclusion that in quadrupeds, the spatial distribution of the magnitude of this activity mirrors the spatial distribution of the magnitude of the muscle inspiratory mechanical advantage.

As is the case for the external intercostal inspiratory activity, internal intercostal expiratory activity in the dog decreases from the dorsal to the ventral portion of the rib cage (Fig. 14). In contrast to external intercostal activity, however, internal intercostal expiratory activity in the dorsal portion of the rib cage is greatest in the caudal interspaces and decreases gradually in the rostral direction (135). In the dog, in fact, the internal interosseous intercostals in the middle and ventral portions of the most rostral segments remain electrically silent during breathing, including when the expiratory drive to the muscles is increased by CO_2-enriched gas mixtures or by expiratory threshold loads. Such a caudorostral gradient was also described qualitatively in the cat (5, 92, 118). Thus the spatial distribution of the magnitude of internal intercostal expiratory activity mirrors the spatial distribution of the magnitude of the muscle expiratory mechanical advantage.

The canine parasternal intercostals also show prominent gradients of activity. Specifically, in the dog, inspiratory activity in a particular parasternal intercostal is greatest in the muscle bundles situated in the vicinity of the sternum, and it decreases progressively in the lateral direction such that the muscle bundles near the chondrocostal junctions remain consistently silent (50). In agreement with this gradient of inspiratory activity, measurements of the uptake of the glucose tracer analog [^{18}F]fluorodeoxyglucose in the canine parasternal intercostals have shown a prominent mediolateral gradient of metabolic activity in these muscles during resting breathing (136). In addition, inspiratory activity and, with it, metabolic activity in the medial parasternal bundles is greatest in the second through the fifth interspaces and decreases from the second to the first interspace and from the fifth to the eighth interspace (134, 136). Thus, as is the case for both the external intercostals and the internal interosseous intercostals, the spatial distribution of neural drive

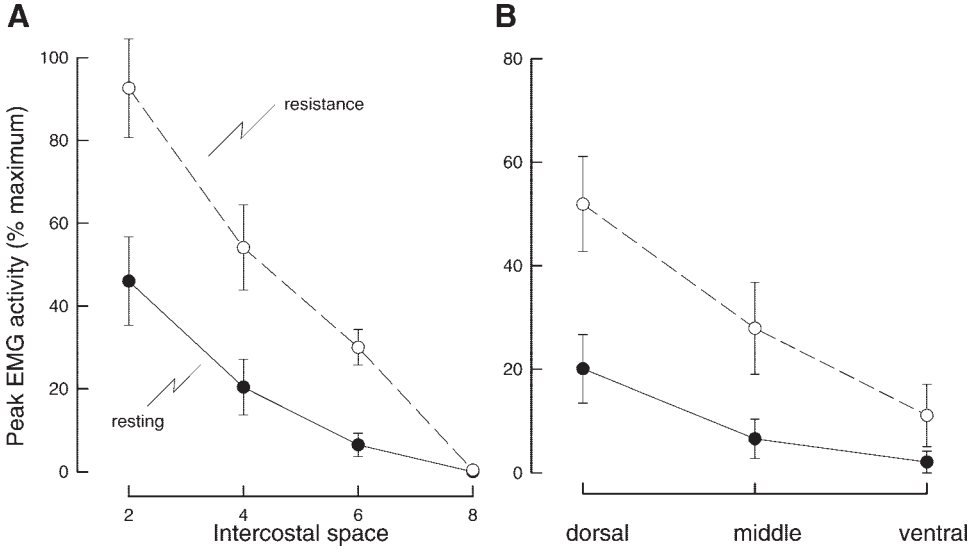

FIG. 13. Spatial distribution of external intercostal inspiratory activity in dogs. The closed circles are the mean ± SE values obtained during resting breathing in eight animals; the open circles are the corresponding values during breathing against an elevated inspiratory airflow resistance. *A*: activity recorded from the dorsal third of the second, fourth, sixth, and eighth interspaces. *B*: activity recorded from the dorsal third, the middle third, and the ventral third of the fourth interspace. Each activity is expressed as a percentage of the activity recorded during tetanic, supramaximal stimulation of the external intercostal nerve (maximal activity). Note that the amount of external intercostal inspiratory activity decreases progressively from the second to the eighth interspace (*A*) and from the dorsal to the ventral portion of the rib cage (*B*). [Adapted from Legrand and De Troyer (135).]

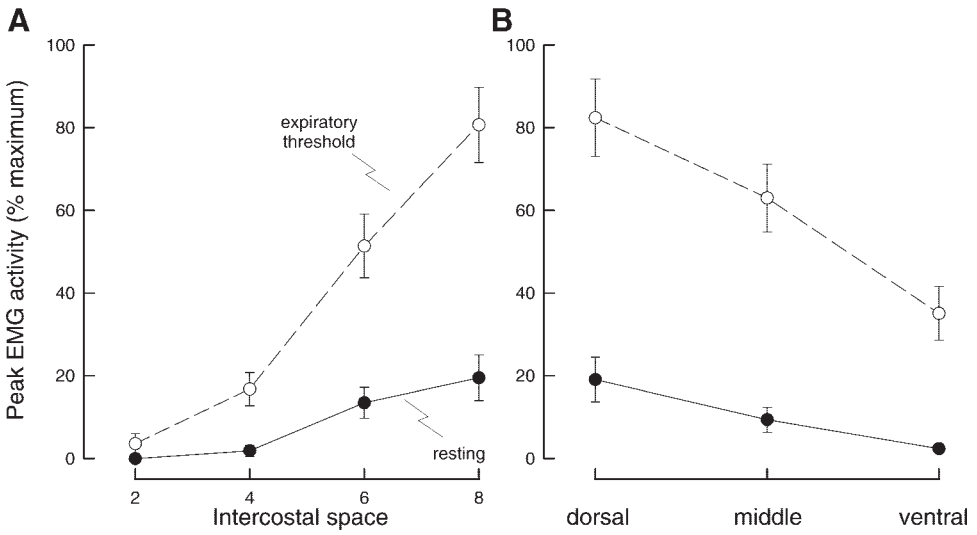

FIG. 14. Spatial distribution of internal intercostal expiratory activity in dogs. The closed circles are the mean ± SE values obtained during resting breathing in nine animals; the open circles are the values obtained during breathing against a positive end-expiratory pressure of 20 cmH_2O (expiratory threshold load). *A*: activity recorded from the dorsal third of the second, fourth, sixth, and eighth interspaces. *B*: activity recorded from the dorsal third, the middle third, and the ventral third of the eighth interspace. Each activity is expressed as a percentage of the activity recorded during tetanic, supramaximal stimulation of the internal intercostal nerve (maximal activity). Note that the amount of internal intercostal expiratory activity also decreases from the dorsal to the ventral portion of the rib cage (*B*) but increases from the second to the eighth interspace (*A*). [Adapted from Legrand and De Troyer (135).]

among the canine parasternal intercostals matches the spatial distribution of mechanical advantage.

Electrical recordings from the levator costae in prone suspended cats, however, have led Hilaire et al. (100) to conclude that inspiratory activity is greater in the muscles of the caudal interspaces than in those of the rostral interspaces, and this would suggest that the topographic distribution of neural drive to this muscle is opposite to the topographic distribution of mechanical advantage. It should be stressed, however, that Hilaire et al. (100) did not normalize electrical activity. Therefore, the differences observed between the levator costae activity in the different interspaces during breathing were qualitative, and they may have been the result of differences in muscle mass and motor unit number, rather than in neural drive.

B. Distribution of Neural Drive in Humans

Using concentric needle electrodes, Taylor (197) has performed extensive electromyographic recordings from the intercostal muscles in healthy individuals, and he concluded that as in the dog and in the cat, the external intercostals and parasternal intercostals in humans are active only during inspiratory efforts and that the internal interosseous intercostals are active only during expiratory efforts. Taylor (197) further noted that during resting breathing, inspiratory activity is limited to the parasternal intercostals while expiratory activity is detected only in the internal interosseous intercostals of the ventrolateral portion of the caudal interspaces, i.e., in the areas where the muscles have the greatest expiratory mechanical advantage. The presence of phasic inspiratory activity in the human parasternal intercostals during resting breathing has since been confirmed in a number of studies (31, 38, 85, 204).

Although Taylor (197) recorded no activity from the external intercostals during resting breathing, he hardly investigated the dorsal portion of the rostral interspaces, i.e., the areas where the external intercostals have the greatest inspiratory mechanical advantage and the greatest inspiratory effect (Fig. 10). The distribution of inspiratory drive to the human external intercostal muscles was recently examined in greater detail by implanting monopolar electrodes under ultrasound guidance in six healthy individuals (45). Electromyographic recordings were obtained from different muscle areas, in particular in the dorsal portion of the rib cage, during resting breathing, and representative records are shown in Figures 15 and 16. The external intercostals in the dorsal portion of the third and fifth interspaces, in fact, showed phasic inspiratory activity with every breath in every subject. In contrast, the muscle in the ventral portion of the third interspace showed phasic inspiratory activity in only three of six subjects, and the muscle in the dorsal portion of the seventh interspace was almost invariably silent. In addition, activity in the ventral portion of the third interspace, when present, and activity in the dorsal portion of the fifth interspace were delayed relative to the onset of activity in the dorsal portion of the third interspace. The discharge frequency of single motor units in the dorsal portion of the third interspace also averaged 11.4 ± 0.3 Hz and was, therefore, similar to the discharge frequency of diaphragmatic motor units. On the other hand, the inspiratory modulation of the motor units recorded from the ventral portion of the third interspace and the dorsal portion of the fifth interspace was much smaller, averaging only 6.0 ± 0.5 and 6.7 ± 0.4 Hz, respectively. The conclusion clearly emerges, therefore, that the spatial distribution of neural inspiratory drive to the external intercostal muscles in humans also takes place along dorsoventral and

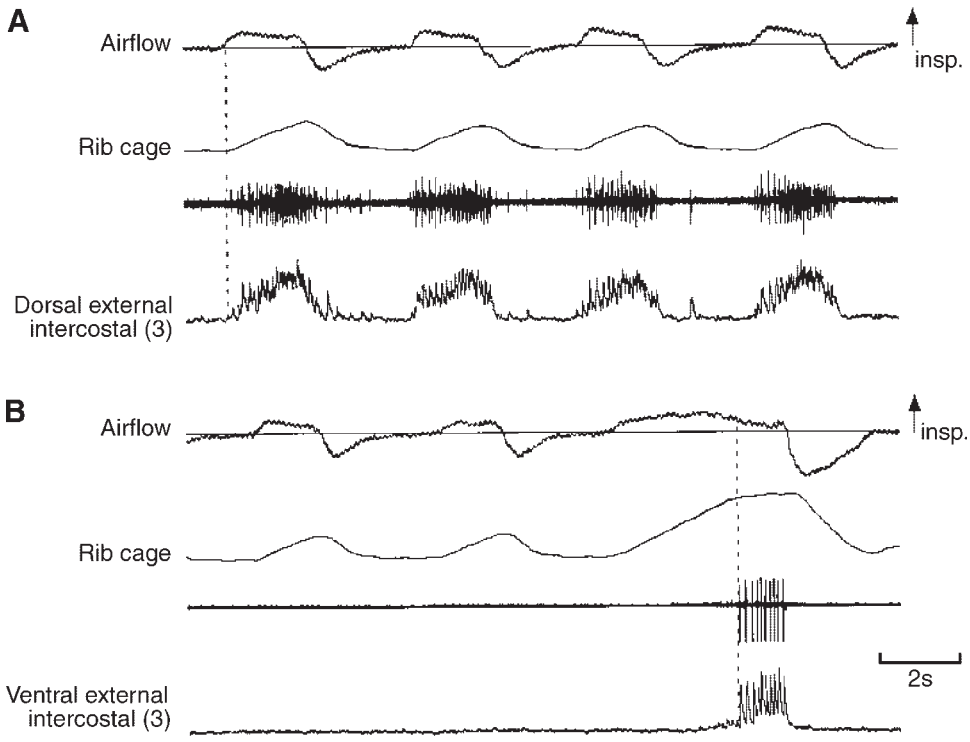

FIG. 15. Examples of EMG activity recorded from the dorsal and ventral portions of the external intercostal muscle in the third interspace in a healthy individual. *A*, from *top* to *bottom*: traces of airflow, changes in rib cage cross-sectional area (increase upward), and raw and integrated EMG activity recorded during resting breathing from the dorsal portion of the external intercostal muscle in the third interspace. *B*: traces obtained during recording from the ventral portion of the muscle in the same subject. The dorsal portion of the muscle (*A*) shows multiunit activity in phase with inspiration and only slightly delayed relative to the onset of inspiratory airflow (vertical dashed line). However, the ventral portion of the muscle (*B*) is electrically silent during resting breathing and fires only at the end of a large, voluntary inspiration (third breath in *B*). [From De Troyer et al. (45).]

rostrocaudal gradients and is matched to the distribution of inspiratory mechanical advantage.

Electromyographic recordings from the human levator costae muscles were obtained in a single subject in the standing posture (89). As for the external intercostal in the ventral portion of the third interspace, the levator costae commonly showed phasic inspiratory activity superimposed on tonic activity, thus suggesting that neural drive to the muscle is small. However, the study was limited to the ninth and tenth interspaces. Also, no mea-

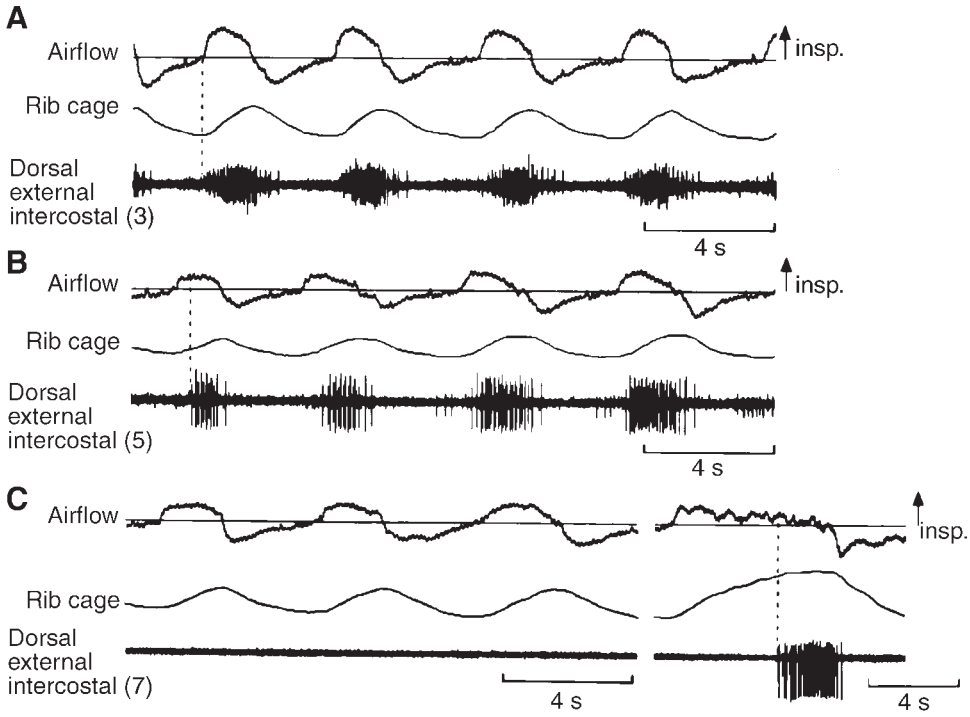

FIG. 16. Examples of EMG activity recorded from the dorsal portion of the external intercostal muscle in the third, fifth, and seventh interspaces in a normal subject. Same conventions as in Fig. 15. As in Fig. 15, the muscle in the third interspace (*A*) shows multiunit activity in phase with inspiration. The muscle in the fifth interspace (*B*) also shows phasic inspiratory activity, but this activity starts later (vertical dashed line) than that in the third interspace relative to the onset of inspiratory airflow. The muscle in the seventh interspace (*C*) is electrically silent during resting breathing (first 3 breaths) and fires only at the end of a large, voluntary inspiration (last breath). [From De Troyer et al. (45).]

surement was made of the timing of levator costae inspiratory activity or of the discharge frequency of the motor units, so no conclusion can be drawn regarding the amplitude and spatial distribution of neural drive to this muscle. Contrary to the dog, the triangularis sterni in humans remains silent during resting breathing and fires only during voluntary and involuntary expiratory efforts (57).

C. Implications

The fact that, in both quadrupeds and humans, the external intercostals are active only during inspiration and that this activity is restricted to areas with an inspiratory mechanical advantage implies that these muscles have an inspiratory function during breathing. Conversely, the internal interosseous intercostals are active only during expiration, and activity is restricted to areas with an expiratory mechanical advantage, so these muscles have an expiratory function. Thus these two sets of muscles, like the parasternal intercostals and the triangularis sterni, have opposite functions.

Furthermore, because the spatial distribution of the level of inspiratory activity in the external intercostals matches the spatial distribution of the magnitude of the muscle inspiratory mechanical advantage, the inspiratory function of these muscles should be greater than it would if the same total amount of activity were uniformly spread over all areas with an inspiratory mechanical advantage. The matching between level of activity and magnitude of mechanical advantage in the internal interosseous intercostals and the parasternal intercostals (at least in the dog, the spatial distribution of parasternal intercostal activity in humans is not known) implies that the respective expiratory and inspiratory functions of these muscles are similarly enhanced. Although it has been suggested that such matching may minimize the work of breathing (50), a formal analysis of this phenomenon has not previously been attempted. The issue will be developed in section VIII.

IV. MECHANISMS FOR THE DISTRIBUTIONS OF NEURAL DRIVE TO THE INTERCOSTAL MUSCLES

Representative records from external intercostal nerve filaments in cats are shown in Figure 17. It is apparent that there is a larger number of active motor units in the rostral (T_3) than in the caudal (T_7) interspace (Fig. 17*A*) and a larger number of active motor units in the dorsal (proximal) than in the ventral (distal) region (Fig. 17*B*) (also see Refs. 26, 123, 124). Similarly, in humans, although individual motor units in the high activity regions may fire faster than in the low activity regions (45), increase in intercostal activity with increased respiratory drive is achieved primarily by motor unit recruitment (84). Thus, in large part, the spatial distribution of intercostal activity is determined by the recruitment order of motor units and, hence, by the recruitment order of motoneurons. To the extent that the output of a motoneuron is determined by its intrinsic properties and synaptic inputs, the spatial distributions of intercostal activity may therefore result from topographic differences in the intrinsic properties of intercostal motoneurons, differences in the synaptic inputs originating from intercostal muscle afferents, or differences in the synaptic inputs from central sources.

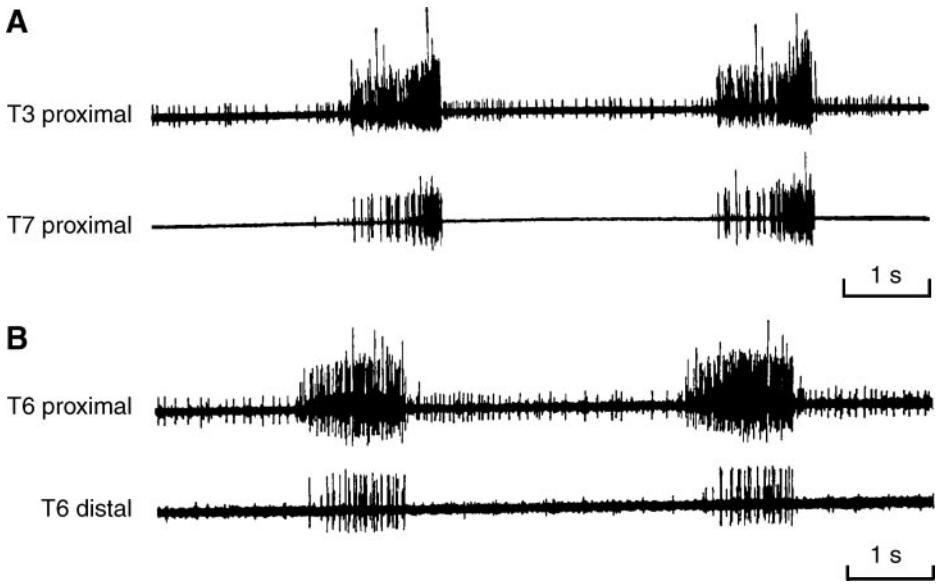

FIG. 17. Efferent discharges from external intercostal nerve filaments in two different anesthetized cats under neuromuscular blockade and artificial ventilation (moderate hypercapnia). Comparison of either the caudal versus rostral filaments in *A* or the distal versus proximal filaments in *B* shows fewer active motor units in the caudal or the distal filament. [Modified from Davies et al. (26) (*A*) and Kirkwood and Sears (123) (*B*).]

A. Intercostal Motor Units

It is well recognized that for most muscles, when activity is driven by synaptic inputs such as in normal motor behaviors, motor units are recruited in a stereotyped order (13). As force is increased, the smallest motor units, those producing the least force, are recruited first. Motor unit size is expressed in a number of parameters, all correlated, including motoneuron size (soma diameter, size of dendritic tree), axon diameter (conduction velocity, electrical threshold, relative spike amplitude), twitch tension, motor unit type, or motoneuron electrical properties, such as input impedance, rheobase (lowest constant current intensity required to elicit repetitive discharge), and duration of afterhyperpolarization. Henneman's "size principle" emphasized motoneuron size, with its definition by Henneman, Somjen, and Carpenter (97) strictly relating the recruitment order to motor axon diameter. However, variations on such a relationship, including extrinsic factors, such as variations in synaptic input (13), are possible and have been much debated (8, 164).

Recordings from either external intercostal or internal intercostal nerve filaments in the cat show that motor units are recruited more or less in order of spike amplitude as the ramplike increase in inspiratory or expiratory drive progresses during inspiration or expiration, respectively (26, 124, 126, 127, 188), or as the chemical drive to breathe is increased (188). Moreover, in any undissected (i.e., naturally occurring) intercostal nerve branch, the relative amplitudes of the extracellularly recorded spikes are closely related to the axon diameter. Thus the size principle does appear to operate within small regions of intercostal muscle. However, such recordings also suggest that this principle is not a major determinant of the spatial distributions of intercostal activity. Indeed, when recordings between filaments of apparently similar thickness in "low-threshold" and "high-threshold" regions are compared (Fig. 17), the unit spikes recruited in the high-threshold regions are not obviously larger than those in the "low-threshold" regions, and spike amplitudes within similar ranges are successively recruited in the two filaments. Although comparisons between different filaments cannot be made on the same basis as within a single-filament recording, confidence in these observations can come from the "calibration" of the spike amplitudes provided by the frequently associated gamma discharges (187, 188).

Considerations of the fiber type composition of intercostal muscles similarly led to the idea that the size principle is not the primary determinant of the spatial distributions of intercostal activity. The external and internal intercostal muscles are mixed muscles (2) and contain both slow motor units, made up of slow-twitch oxidative (SO; type I) fibers, and fast motor units, made up of fast-twitch oxidative-glycolytic (FOG; type IIa) or fast-twitch glycolytic (FG; type IIb) fibers (68). There is substantial evidence that SO motor units are innervated by small low-threshold motoneurons, whereas FOG and FG motor units are, in general, innervated by large higher-threshold motoneurons (13, 14, 182). Greer and Martin (92) studied the histochemical properties of intercostal muscles in the cat, and they found a correlation between the fiber type composition and the activity pattern. Specifically, the parasternal intercostals and the external intercostals in the dorsal portion of the rostral interspaces had a higher proportion of SO fibers than the other areas of external intercostal (50–55 vs 35%). The external intercostals in the dorsal portion of the rib cage also showed a progressive rostrocaudal decrease in the proportion of SO fibers, in agreement with the observed distribution of inspiratory activity during breathing. However, the fiber type distribution in the internal intercostals was uniform throughout the rib cage and did not correspond to the caudorostral gradient of expiratory activity. The parasternal intercostal muscles in the dog also have a uniform distribution of fiber types with 55–60% of SO fibers and 40–45% of FOG fibers, in contrast to the prominent mediolateral gradient of inspiratory activity (52), and the motoneurons innervating the medial and lateral parasternal muscle bundles have similar sizes and similar morphologies (212). In the rat, Hardman and Brown (96) similarly reported no difference in motoneuron size between distal and proximal intercostal muscles and "a fairly uniform distribution of different muscle fiber types" except for the most proximal part of the external intercostal muscle containing "a much higher proportion of type I fibers." Finally, in humans, Mizumo and Secher (161) found a similar proportion of SO fibers (60–65%) in the external intercostals of the dorsal and ventral portions of the fifth interspace, the parasternal intercostal of the third interspace, and the external intercostal of the eighth interspace; the internal interosseous intercostals in the fifth and eighth interspaces also had the same proportion of SO fibers. On the basis of these observations, the conclusion therefore emerges that the topographic distributions of intercostal activity are most likely related to the distributions of synaptic inputs.

B. Peripheral Inputs to Intercostal Motoneurons

Motor discharges in the external intercostal and levator costae muscles in cats, rabbits, and dogs are commonly reduced or abolished after section of the thoracic dorsal roots (32, 100, 184, 188, 193). In contrast, motor discharges in the canine parasternal intercostals are unaltered (32). Also, when the normal inspiratory cranial displacement of the ribs in dogs is enhanced by an external force, parasternal intercostal activity remains un-

changed, whereas activity in the rostral external intercostals and levator costae is reflexly reduced (34). These observations suggest that inputs from intercostal muscle afferents contribute to intercostal efferent activity, and indeed, the intercostal muscles have a similar afferent innervation as the limb muscles (146), with typical complements of muscle spindles (primary and secondary endings), Golgi tendon organs, and, at the costovertebral junctions, joint receptors.

The external and internal interosseous intercostals in the cat are richly endowed with muscle spindles (72), and the studies of Crichlow and von Euler (21) and Sears (187, 188) have established that the motor drive to these receptors (i.e., the fusimotor drive) is modulated by the act of breathing. This indicates that these spindles have a specific function in respiratory movements and not just a role in other movements such as posture or locomotion (18, 28, 71). On the other hand, the parasternal intercostals have a particularly low density of muscle spindles, and the triangularis sterni has an even lower density, similar to the diaphragm. Such differences are consistent with the differential responses of the external and parasternal intercostal muscles to dorsal rhizotomy and to cranial rib displacement. Moreover, the external intercostals in the cat show a rostrocaudal gradient of spindle density (72), and it would therefore be tempting to relate this gradient to the rostrocaudal gradient of external intercostal inspiratory activity. Such a link, however, cannot be made without knowledge of the connections made by spindle afferents.

As for limb muscles, afferents from external and internal intercostal muscle spindles make monosynaptic connections to motoneurons, as demonstrated by the short-latency excitatory postsynaptic potential (EPSP) observed during electrical stimulation of muscle nerves at a low stimulation strength (189). The monosynaptic EPSP induced by stimulation of the external intercostal nerve in the same segment, however, has a small amplitude, rarely above 1 mV. This is much smaller than the 5–10 mV typical of EPSPs in large hindlimb muscles (74). In fact, the EPSP derived from any one spindle afferent in an external intercostal motoneuron in the same segment is, on average, similar in amplitude to that for hindlimb muscles, but even though the external intercostals have a relatively high spindle density, their mass is small and the total number of spindle afferents per segment is also small, resulting in the small EPSP during nerve stimulation (121, 122). The contribution of spindle inputs to the natural respiratory drive in external intercostal motoneurons has also been estimated on the basis of the strength of the connections, of the convergence of spindle afferents from different segments (two adjacent segments plus the same segment), and of the spindle firing rates (121, 122). This calculation indicated that the mean depolarization derived from the monosynaptic spindle inputs is low ($\simeq$1 mV) and represents only a small proportion of the total depolarization a motoneuron needs to reach threshold (10–15 mV). Although the calculation could not consider the potential topographic variations in the parameters, such a small proportion suggests that spindle afferent inputs are not the primary determinants of the spatial distribution of external intercostal activity. This proportion, however, could still provide a useful control signal (191), either by increasing motoneuron firing rate (91) or by recruiting some motoneurons into firing.

Sears (189, 191) reported larger EPSPs for the internal intercostal motoneurons than for the external intercostals. He also reported a spread of connections to the motoneurons in two adjacent segments. The stimulation, however, was applied to the whole internal intercostal nerve, so neither the muscle innervated by the motoneurons nor the muscle supplying the afferents (intercostal or abdominal) was identified (see sect. IA). Kirkwood and Sears (120) have confirmed that spindle afferents (both primary and secondary endings) from the internal intercostal muscle cause monosynaptic EPSPs, but the motoneurons were not identified any more closely than by Sears. The potential role of the direct inputs from spindle afferents in generating the spatial distribution of internal intercostal expiratory activity, therefore, cannot be readily assessed.

By analogy with what is known from hindlimb muscles (150), one would also expect indirect (di- or polysynaptic) connections from intercostal spindle afferents. In fact, spindle afferent terminations outside the motor nuclei are present in the thoracic spinal cord (165), and some evidence for disynaptic excitation modulated with respiration has been obtained in EPSPs induced by spindle afferents in external intercostal motoneurons (121, 125). Such indirect connections, however, have hardly been explored. Similarly, although observations in dogs have suggested that receptors in the costovertebral joints, as described by Godwin-Austin (88) in cats, may modulate external intercostal and levator costae inspiratory activity (35), the role played by these receptors in determining the spatial distributions of intercostal activity is unknown. The role of intercostal tendon organs is also unknown, but it should be emphasized that these may well contribute excitation during breathing. Indeed, evidence from hindlimb muscles in the decerebrate or spinal cat indicates that the circuits involved in these afferent inputs are reconfigured when the muscle becomes active, and the classic disynaptic inhibition of homonymous motoneurons (75, 132) can be replaced by excitation (90, 150, 171). The spatial distributions of intercostal activity, therefore, might involve not just the basic connections of tendon organs, but also how these may be configured for the active versus inactive muscle areas.

Irrespective of these unknowns, it is of particular interest that the mediolateral and rostrocaudal gradients

of inspiratory activity in the canine parasternal intercostals remain unchanged after bilateral section of the thoracic dorsal roots (52, 134). More importantly, it is a fact that the overall distributions of external and internal intercostal activity in awake seated humans, in anesthetized supine dogs, and in anesthetized prone cats are similar. The spatial distributions of intercostal activity in artificially ventilated animals with neuromuscular blockade (e.g., Ref. 125) are also very similar to those in spontaneously breathing animals (5, 135). The conclusion must be drawn, therefore, that these distributions have a core component that is independent of peripheral afferent inputs and is centrally generated.

C. Central Inputs to Intercostal Motoneurons

The central drive to intercostal motoneurons can be examined independently of peripheral afferent inputs by making recordings with the animal paralyzed and mechanically ventilated. Under these conditions, the signal that is the immediate precursor of the intercostal motoneuron discharges is a waxing and waning of motoneuron membrane potential, the central respiratory drive potential (CRDP, 190). Figure 18 shows examples of CRDPs in inspiratory and expiratory intercostal motoneurons. For each type of motoneuron, this potential has an excitatory ramp of depolarization, corresponding to the ramplike pattern of efferent discharges seen in the corresponding muscle, followed by a ramplike (incrementing) phase of inhibition. The depolarizing ramps, if large enough, could act alone to produce the respiratory discharges or, alternatively, they may add to a nonrespiratory (tonic) depolarization from other sources (192).

The respiratory pattern generator resides in the medulla (81), and its output is conveyed to the spinal cord by the respiratory bulbospinal neurons, either inspiratory (IBSNs), in the dorsal respiratory group (DRG) or the ventral respiratory group (VRG), or expiratory (EBSNs) in the VRG. These neurons show ramplike patterns of activity that are similar to the CRDPs in intercostal motoneurons, and anatomical tracer experiments support the existence of direct (monosynaptic) connections from these neurons to the intercostal motoneurons (162). For the present purposes, however, specific, quantitative assessments of functional connections are required (116). These measurements are of two types: intracellular spike-triggered averaging (STA), which reveals single-fiber EPSPs in individual motoneurons, and cross-correlation of spike discharges, which reveals the increased probability of motoneuron firing during the rising phases of such EPSPs (Fig. 19). The two types of measurement are formally similar, but they differ considerably in the motoneuron sampling (114, 123). Specifically, cross-correlation samples only those motoneurones that are spontaneously active and has, therefore, a bias toward the earliest recruited motoneurones, whereas with STA, the bias is toward the largest, highest threshold motoneurons, which are more likely to give stable intracellular penetrations.

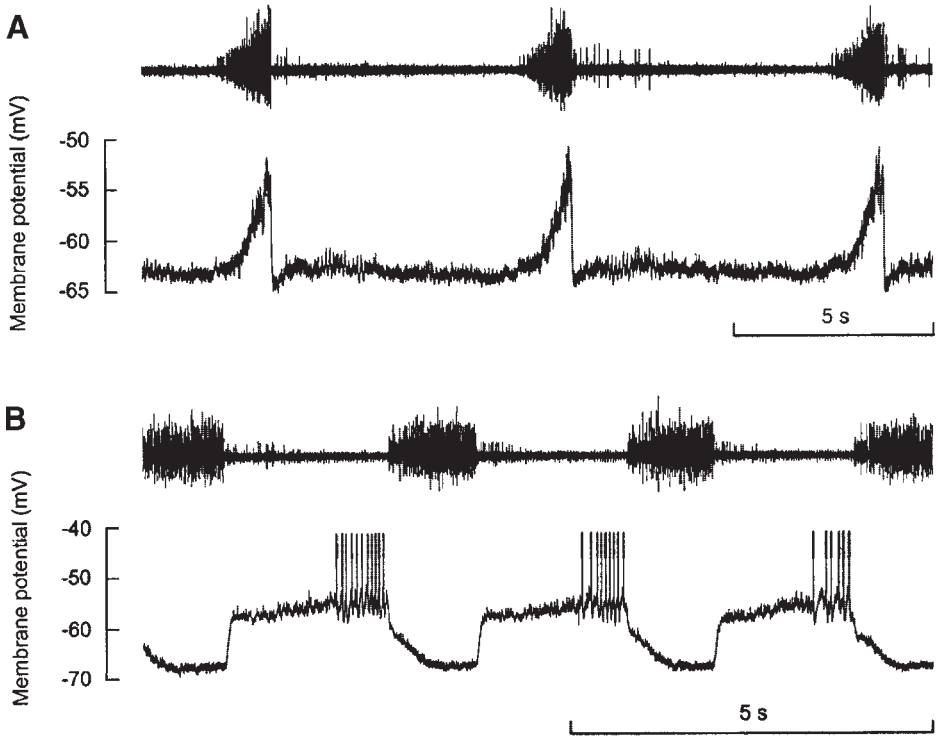

FIG. 18. Central respiratory drive potentials in intercostal motoneurons in the anesthetized cat. *A*: inspiratory motoneuron with its axon in the internal intercostal nerve of T_8, presumably innervating the parasternal intercostal muscle. *B*: expiratory motoneuron innervating part of the dorsal portion of the internal interosseous intercostal muscle of T_8. *Top trace* in each case is a recording of the efferent discharge of the external intercostal nerve of T_6, as a marker of inspiration. Note that the motoneuron in *A* is not firing (membrane potential always more negative than −51 mV). The motoneuron in *B* only fires towards the end of expiration (spikes truncated). [Data from Anissimova et al. (3).]

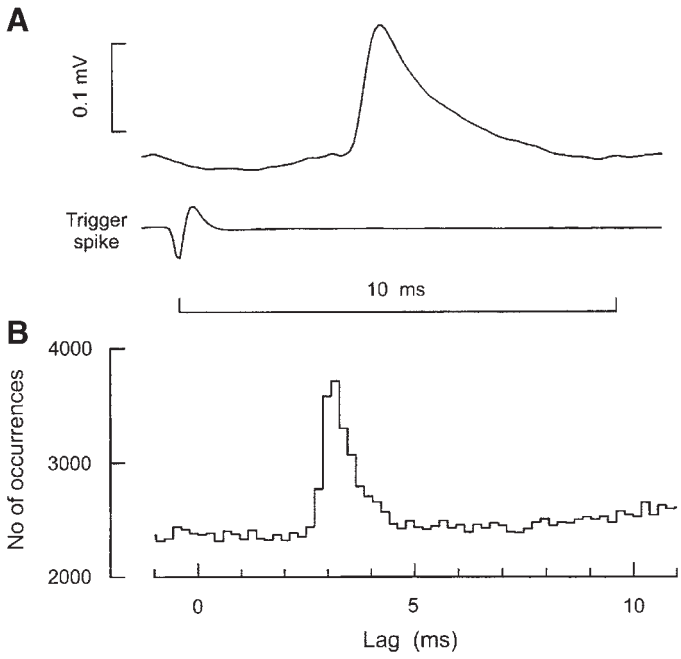

FIG. 19. Measurements of direct connections from the medulla to internal intercostal motoneurons in the anesthetized cat. *A*: spike-triggered average excitatory postsynaptic potential (EPSP) derived from an expiratory bulbospinal neuron (EBSN) and recorded in an expiratory motoneuron innervating part of the dorsal portion of the internal interosseous intercostal muscle of T_8. *B*: cross-correlation histogram between the discharges of an EBSN and of a dorsal internal intercostal nerve filament at T_8. Zero lag is the time of the reference spikes from the EBSN. The peak in *B* appears at an earlier latency than the EPSP in *A* because the conduction velocity of the EBSN was greater (69.1 vs. 39.5 m/s). [Data from Anissimova et al. (3) (*A*) and Road and Kirkwood (178) (*B*).]

In spite of this difference, the two methods have provided rather similar results. For IBSNs in the VRG and external intercostal motoneurons, there is agreement that the direct connections are weak (27, 156). For IBSNs in the DRG, Davies et al. (27) using cross-correlation found similarly weak connections. On the other hand, Duffin and Lipski (70) using STA found rather strong connections (EPSPs in 9 of 32 pairs), and they concluded that inspiratory intercostal motoneurons have stronger connections from the DRG than from the VRG, consistent with the conclusions of Fedorko et al. (80) for the phrenic motoneurons. It should be pointed out, however, that the observations of Duffin and Lipski (70) were dominated by inspiratory motoneurons identified from the internal intercostal nerve, i.e., parasternal intercostal motoneurons (7 of 25 with EPSPs), whereas the findings of Merrill and Lipski (156) and those of Davies et al. (27) were restricted to external intercostal motoneurons. The difference reported by Duffin and Lipski (70), therefore, might be interpreted as a difference between two motoneuron populations, rather than between two groups of IBSNs in the medulla, and this would suggest that, as for the diaphragm (see Ref. 162 for references), an important factor contributing to the consistent inspiratory activity in the parasternal intercostals is a relatively strong monosynaptic drive from the medulla. Measurements of motoneuron synchronization by Vaughan and Kirkwood (201) also support this idea, in that phrenic motoneurons and parasternal intercostal motoneurons receive common monosynaptic inputs (i.e., inputs from axons which branch to make direct connections to both groups of motoneurons). In contrast, common inputs to either phrenic or parasternal intercostal motoneurons and external intercostal motoneurons are asymmetric, being monosynaptic to the former, but largely disynaptic to the latter.

To the extent that the measurements reported by Davies et al. (27) of the connections between IBSNs in the DRG and the external intercostal motoneurons were made using external intercostal discharges in up to six interspaces, they have direct relevance to the rostrocaudal gradient of external intercostal inspiratory activity. Individual IBSNs did appear to differ in the overall strength of their connections. However, no consistent differences were identified between the different thoracic segments (T_2-T_9), and units did not appear to be specialized in giving connections to adjacent segments or close groups of segments. Because the technique used in this study was cross-correlation, however, the measurements were restricted to firing motoneurons, and differences between these motoneurons and those innervating silent areas could not show up. Moreover, as for the spindle afferent inputs, the total average depolarization generated by the direct connections from IBSNs was estimated to be only ≃1 mV. With such a small contribution, a grading of inputs appropriate to the rostrocaudal gradient would have been unlikely. In this respect, it should be stressed that CRDPs of up to 15 mV have been recorded in both external intercostal (125, 156) and parasternal intercostal (Fig. 18) motoneurons and that the main part of these CRDPs consists of an inspiratory ramp. Consequently, the main part of the unidentified input is likely to be an inspiratory-phased, rather than a tonic, signal and, hence, the signal responsible for the spatial distribution of inspiratory activity would be inspiratory-phased as well.

The situation for expiratory connections is different. Direct connections between EBSNs and thoracic expiratory motoneurons were demonstrated by Kirkwood and Sears (119) and Cohen et al. (20). Merrill and Lipski (156), using intracellular STA, found very few connections (2 of 57 EBSN/motoneuron pairs), but Kirkwood and colleagues (115, 116), using both cross-correlation and STA, subsequently confirmed that such connections are common and strong, ≃10 times stronger than found by Merrill and Lipski (156). Strong connections were also observed recently by Anissimova et al. (3) in a general survey both of motoneurons innervating relatively rostral interspaces (T_5, T_6) and of motoneurons innervating more caudal interspaces (T_7-T_9). Motoneurons in both areas, including

those specifically innervating the dorsal half of the internal intercostal muscles in caudal interspaces, received connections (Fig. 19*A*). No evidence was found in support of a relationship between these connections and the spatial distribution of expiratory activity, although the survey was not detailed enough to investigate fully such a relationship.

The maximum size of the CRDPs observed in expiratory motoneurons by Merrill and Lipski (156) and Anissimova et al. (3) was ≃10 mV. Furthermore, a significant part of these potentials can be the result of an inhibition caused by inspiration (190); this part is particularly apparent in the example shown in Figure 18*B*. In fact, the expiratory depolarizing ramp, which may be a better assessment of the expiratory excitation, was only 6 mV or smaller (3). In contrast to the inspiratory motoneurons, therefore, a considerable fraction of the excitatory input needed to depolarize expiratory motoneurons to threshold, and which may contain the control signal for the spatial distribution, could be derived from tonic activity. Nevertheless, for both inspiratory and expiratory motoneurons, it appears that synaptic inputs from bulbospinal neurons and intercostal muscle afferents do not provide sufficient motoneuron depolarization.

It is reasonable to speculate that the missing part of this depolarization originates from interneurons. On general anatomical grounds, segmental interneurons are known to provide the majority of motoneuron inputs (152). In the cat, large numbers of respiratory interneurons with either inspiratory or expiratory firing patterns have been described in the thoracic spinal cord (117) and others in the lower cervical segments (7, 66, 170). Inspiratory interneurons have also been described in the upper cervical segments of the cat (4, 140) and of the rat (141). These upper cervical interneurons appear to receive direct excitation from IBSNs (101, 102, 199) and have descending axons, including some arborizations in thoracic segments (103, 140).

Hardly any direct connections between thoracic or cervical interneurons and intercostal motoneurons have yet been identified (67, 103, 118, 128, 198). However, because the numbers of such interneurons are so large (117), it is a major task to obtain a sufficient sample to identify fully which of these connect to motoneurons. Moreover, extracellular measurements have shown that the vast majority of individual thoracic interneurons produce relatively weak effects at any given location (128), and intracellular labeling has confirmed that such interneurons, many of which have long descending axons, show few, relatively sparse axon collateral branches, as illustrated in Figure 20 (186). It is most likely, therefore, that the excitatory input from spinal interneurons to intercostal motoneurons is transmitted by large numbers of neurons, each with individually weak, but widely distributed connections, but whether this excitatory input differs between the different regions of the thorax is unknown.

D. Inhibitory and Modulatory Mechanisms

To close this section, it should be pointed out that the spatial distributions of intercostal activity do not necessarily involve differences in excitatory synaptic input. Differences in an inhibitory drive could achieve the same result, either by sculpting the CRDP from an ongoing tonic drive or by selectively modulating a universally distributed phasic input. And indeed, McCrimmon et al. (151) have recently described a GABA-mediated mechanism where the excitatory drive in a wide range of respiratory neurons may be modulated without any change in time course, i.e., the apparent operation of a "gain control." Intrinsic amplification of synaptic signals would still be another possibility. One mechanism receiving a great deal of attention at present is related to persistent inward currents (PICs) carried by Ca^{2+} channels, particularly in motoneuron dendrites (105); such currents are consid-

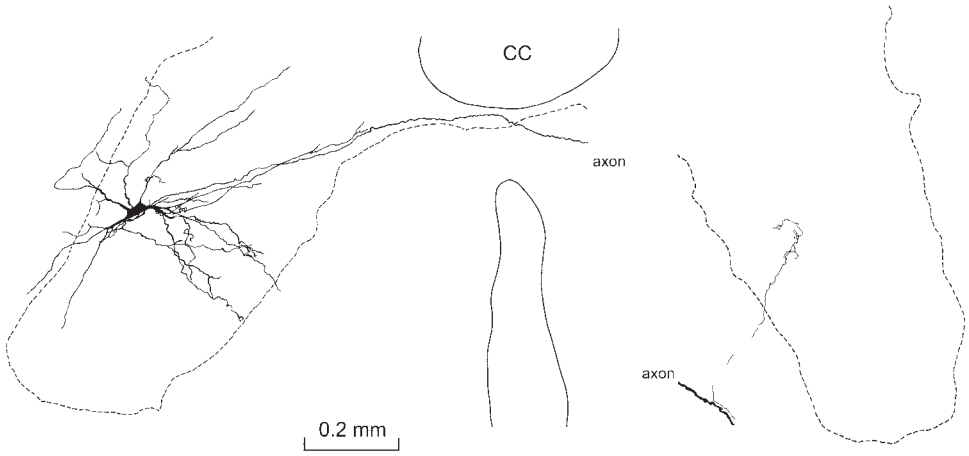

FIG. 20. A thoracic interneuron in the cat, intracellularly labeled with Neurobiotin and histologically reconstructed. The neuron was recorded in the left ventral horn of T_8. The axon crossed 0.25 mm rostral to the soma and descended 7.75 mm before giving the illustrated collateral to the right ventral horn, then a further 3.1 mm before giving another similarly sparsely branched collateral to the same ventral horn region. [Previously unpublished data from Saywell et al. (186).]

ered by many investigators as being necessary to produce strong discharge in most motoneurons (173). The speculation could be offered, therefore, that motoneurons innervating different areas of the intercostal musculature would have either different complements of Ca^{2+} channels or different degrees of modulation of the PICs by descending monoaminergic systems. The observation that the motoneurons innervating the medial and lateral parts of the canine parasternal intercostals have different serotonergic inputs (212) supports this latter possibility, serotonin being well known as a modulator of PICs. Other modulatory inputs, however, can influence motoneurons (173, 175) and could also be involved in the topographic distributions of intercostal activity.

V. MECHANICAL INTERACTIONS AMONG THE INSPIRATORY INTERCOSTAL MUSCLES

A. Interactive Effects on Rib Cage Displacement

Although the mechanisms for the distributions of neural drive among the intercostal muscles remain uncertain, two sets of muscles, namely, the parasternal intercostals and the external intercostals in the dorsal portion of the rostral interspaces (together with the levator costae), thus contribute to the inspiratory expansion of the lung. This expansion is the result of the action of the muscles on the ribs. In fact, the ribs provide the solid structural elements that are needed to transform tension in the external and parasternal intercostal muscles into lung expansion. Cappello and De Troyer (17) have clearly shown this essential role of the ribs by removing the bony ribs on both sides of the chest in dogs; the lateral walls of the rib cage in these animals were therefore made simply of bands of periosteum connected by intercostal muscles. With the removal of the ribs, the fall in P_{ao} produced by contraction of the parasternal intercostals was markedly reduced and that produced by contraction of the external intercostals was reversed into a pressure rise.

When either the external or the parasternal intercostal muscle in a single interspace is selectively activated by electrical stimulation in the dog, the upper and lower ribs of the interspace move closer together, but the cranial displacement of the lower rib is greater than the caudal displacement of the upper rib (46, 48, 169). Also, when either set of muscles contracts in isolation in all interspaces, all the ribs are displaced in the cranial direction, thus confirming that the two muscles have an inspiratory action on the ribs (41, 58, 143). As shown in Figure 21, however, the two muscles drive the ribs along different trajectories. Specifically, when the parasternal intercostals in all interspaces are bilaterally denervated in dogs with diaphragmatic paralysis, such that the external intercostals and levator costae are the only muscles active during inspiration, the cranial displacement of the ribs is substantially greater than their outward displacement relative to the rib trajectory during passive inflation (Fig. 21*A*). In contrast, when the parasternal intercostals in dogs with diaphragmatic paralysis are maintained intact and the external intercostals and levator costae in all interspaces are excised, such that the parasternal intercostals are the only muscles active during inspiration, the outward displacement of the ribs is greater than their cranial displacement relative to the relaxation trajectory (Fig. 21*B*). Yet, during spontaneous breathing, when both the external intercostals and the parasternal intercostals contract together in a coordinated manner, the trajectory of the ribs lies very near their relaxation trajectory.

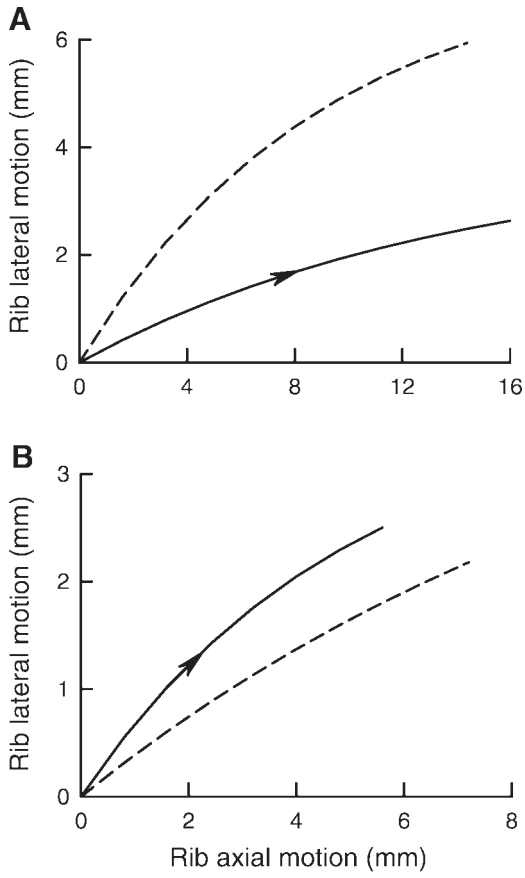

FIG. 21. Patterns of rib displacement produced by the external and parasternal intercostals in the dog. In the animal in *A*, the parasternal intercostals in interspaces 1–8 were denervated on both sides of the sternum; in the animal in *B*, the parasternal intercostals were intact but the external intercostals in interspaces 1–8 were excised. Both animals had a complete diaphragmatic paralysis. The dashed line in each panel is the trajectory of the ribs during passive inflation (relaxation), and the solid line with the arrowhead corresponds to a spontaneous inspiration. [Redrawn from De Troyer and Wilson (58).]

Loring (142), using a finite element model, inferred that the parasternal intercostals in humans also displace the ribs cranially and outward and that the external intercostals displace the ribs only cranially, and measurements

of the changes in rib cage dorsoventral and lateral diameters in seated normal subjects have shown that the displacements of the rib cage during resting breathing are similar to its displacements during passive inflation (39, 130, 149, 177). Thus both in the dog and in humans, the coordinated activation of the two sets of inspiratory intercostals during breathing drives the ribs along a trajectory that matches the relaxation trajectory and thereby reduces the work of breathing (1, 153).

The two sets of muscles also displace the sternum differently. Because the parasternal intercostals run obliquely in the caudal-lateral direction from the sternum to the costal cartilages, their isolated contraction in one or two interspaces in the dog causes not only a cranial and outward displacement of the ribs but also a caudal displacement of the sternum (46). In contrast, the external intercostals act on the sternum through their action on the ribs, so their isolated contraction displaces the sternum in the cranial direction (41, 58). The sternum in the dog also moves in the cranial direction during passive inflation, but it moves in the caudal direction during spontaneous inspiration; such an inspiratory caudal displacement of the sternum and a similar difference compared with passive inflation was also reported in the cat (25). Thus, in quadrupeds, coordinated intercostal muscle activation during breathing drives the ribs but not sternum along the relaxation trajectory, and this distortion implies an increase in the work of breathing and an additional energy expenditure. In humans, however, such a distortion of the rib cage does not occur and the sternum moves in the cranial direction during both spontaneous inspiration and passive inflation (39), as discussed below.

B. Interactive Effects on the Lung

The length-tension characteristics of the parasternal and external intercostal muscles indicate that the force developed by a particular muscle in response to a given stimulation is determined by its length (19, 78). To the extent that the different intercostal muscles are interconnected by the ribs, the costal cartilages, and the sternum, it would therefore be expected that the length of a particular muscle and, hence, the force it exerts during contraction would depend not only on the magnitude of activation of the muscle but also on the interactions between the muscle and the other intercostal muscles contracting at the same time and on the forces developed by these other muscles.

The length interdependences of the intercostal muscles are varied. Because isolated contraction of either the parasternal intercostal or the external intercostal in a single interspace causes a cranial displacement of the lower rib and a caudal displacement of the upper rib (46, 48, 169), contraction of either muscle induces a decrease in length of the other muscle (43). Contraction of the parasternal or external intercostal in a single interspace also displaces the other, more distant ribs, but the magnitude of the displacement decreases as one moves further away from the contracting muscle (95). Consequently, the width of the other interspaces increases and the external intercostals in these interspaces lengthen (43, 61). On the other hand, isolated contraction of the parasternal intercostal in one interspace causes, through the caudal displacement of the sternum (46), a shortening of the parasternal intercostals in the contiguous interspaces (42). In view of these varied length interdependences, it is difficult to predict whether the different inspiratory intercostals would have synergistic or antagonistic interactions on the lung.

As we have pointed out in section II*A*, measurements in dogs have shown that the ΔP_{ao} produced by the simultaneous, bilateral contraction of the parasternal intercostals or external intercostals in two interspaces are nearly equal to the sum of the ΔP_{ao} produced by bilateral contraction of the muscles in each individual interspace (139). The ΔP_{ao} produced by the simultaneous contraction of the parasternal or external intercostals in one or two interspaces on the left and right sides of the sternum are also nearly equal to the sum of the ΔP_{ao} produced by separate left and right contraction (16), thus indicating that the pressure changes generated by the different inspiratory intercostals are essentially additive. Apparently, the changes in length of these muscles are small enough and the muscles remain near enough to their optimal force-producing lengths that the synergistic or antagonistic interactions between them are negligible.

C. Relative Contributions of the External and Parasternal Intercostals to Breathing

The parasternal intercostals in the dog have a greater mass than the external intercostals (see sect. II*B*). Furthermore, the inspiratory mechanical advantage of both muscles decreases in the caudal direction, but the advantage of the parasternal intercostals decreases more slowly than that of the external intercostals (Fig. 5). As a result, although the inspiratory effect of the sternal portion of the parasternal intercostal in the second interspace is only slightly greater than the total inspiratory effect of the external intercostal in the same interspace, the total inspiratory effect of the parasternal intercostals in all interspaces is substantially greater than that of the external intercostals (Fig. 7). In addition, as noted in section V*A*, the canine parasternal intercostals drive the ribs both cranially and outward, whereas the external intercostals drive the ribs primarily in the cranial direction (58, 143), and studies of the relationship between rib displacement and lung volume have shown that in the dog, a given rib

displacement in the outward direction is about four times more effective in increasing lung volume than the same rib displacement in the cranial direction (58). For all these reasons, it would therefore be expected that in this animal, the parasternal intercostals would play a predominant role in the act of breathing.

Several lines of evidence have confirmed that in the anesthetized dog, the parasternal intercostals play a greater role than the external intercostals in displacing the rib cage and the lung during resting inspiration. First, as pointed out in section V*A*, the inspiratory cranial displacement of the ribs in this animal occurs together with a caudal displacement of the sternum, and this sternal displacement entirely results from the action of the parasternal intercostals (46). Second, when the canine parasternal intercostals in all interspaces are denervated on both sides of the sternum, the normal inspiratory cranial displacement of the ribs in the rostral portion of the rib cage is reduced by ~50% despite a two- to threefold compensatory increase in external intercostal inspiratory activity (33, 60). On the other hand, when the canine parasternal intercostals are maintained intact and the external intercostal muscles in all interspaces are excised, parasternal intercostal activity remains unchanged and the inspiratory cranial displacement of the ribs is reduced by only 15–20% (33). Finally, in dogs with diaphragmatic paralysis, denervation of the parasternal intercostals causes a 40% reduction in tidal volume despite a substantial increase in external intercostal activity, whereas excision of the external intercostals leaves both parasternal intercostal activity and tidal volume unaltered (58).

A possible complication to such studies is that anesthesia, in particular barbiturate anesthesia, reduces the amount of inspiratory activity in the external intercostals but has little effect on the activity recorded from the parasternal intercostals (65). Therefore, the possibility exists that the greater contribution of the parasternal intercostals to the rib cage and lung expansion during resting breathing in anesthetized dogs results, at least in part, from anesthesia itself. The relative contributions of the parasternal and external intercostals to the act of breathing in awake animals, however, have not been examined.

Although the external intercostals and parasternal intercostals in humans also drive the ribs along different trajectories (142), the relative effectiveness of cranial versus outward rib displacement in increasing lung volume is unknown. More importantly, in contrast to the dog, the external intercostals in humans are thicker and their mass is much greater than that of the parasternal intercostals (sect. II*D*). As a result, the external intercostal in each interspace down to the sixth has a greater inspiratory effect than the parasternal intercostal (Fig. 11). Also, it is well established that the maximal ΔP_{ao} values produced by the canine external and parasternal intercostal muscles in different interspaces are essentially additive (139), and there is no reason to believe that this principle of pressure superposition does not apply to humans as well. If the ΔP_{ao} values thus shown in Figure 11 are added to each other and multiplied by two for the odd-numbered interspaces, then the total ΔP_{ao} value obtained for all the external intercostals with an inspiratory effect amounts to approximately -15 cmH_2O, whereas the total ΔP_{ao} value for the parasternal intercostals in all interspaces is only -2 to -3 cmH_2O.

Recent electromyographic studies have also shown that during resting breathing in healthy individuals, the external intercostal in the dorsal portion of the third interspace and the parasternal intercostal in the same interspace start firing simultaneously at the onset of inspiration, but the external intercostal motor units fire with greater discharge rates at the peak of inspiration than the parasternal intercostal motor units (11.4 ± 0.3 vs. 8.9 ± 0.2 Hz) (45). Even though the spatial distribution of neural drive to the parasternal intercostals in humans is unknown, it would therefore appear that the inspiratory drive to these muscles could be smaller than that to the external intercostals in the dorsal portion of the rostral interspaces, and this difference, combined with the difference in inspiratory effect, would suggest that in contrast to the dog, the external intercostals in humans make a greater contribution to the act of breathing than the parasternal intercostals. Such a greater external intercostal contribution could account for the fact that the sternum in humans moves cranially, rather than caudally, during inspiration (39), although the inspiratory contraction of the scalenes might also play a role (see sect. VI*A*).

VI. MECHANICAL INTERACTIONS BETWEEN THE INTERCOSTAL AND OTHER RESPIRATORY MUSCLES

A. Interaction Between the Inspiratory Intercostals and the Neck Muscles

We pointed out in section II*A* that two muscles in the neck, namely, the scalenes and the sternomastoids, have an inspiratory mechanical advantage. The scalenes in humans comprise three muscle heads that run from the transverse processes of the lower five cervical vertebrae to the upper surface of the first two ribs, and the sternomastoids run from the mastoid process to the ventral surface of the manubrium sterni and the medial third of the clavicle. The muscles in the dog have a similar overall anatomical arrangement, but the medial head of the scalenes in this animal (the pars supracostalis) descends to the lateral aspect of the sixth to eighth ribs, rather than the first rib (47); in the hamster, this medial head de-

scends only to the third and fourth ribs (82). When the head and the cervical spine are fixed, therefore, isolated contraction of either the scalenes or the sternomastoids in the dog causes a large cranial displacement of the sternum and the ribs and promotes expansion of the rib cage, particularly along its dorsoventral diameter (47). Similarly, contraction of the sternomastoids in humans with transection of the upper cervical cord (such subjects have complete paralysis of the diaphragm, intercostal, abdominal, and scalene muscles, but the sternomastoids, which are primarily supplied by the 11th cranial nerve, are spared and contract forcefully during unassisted inspiration) is associated with a marked cranial displacement of the sternum and a large expansion of the rostral portion of the rib cage (24, 40, 69).

The scalenes and sternomastoids have traditionally been regarded as "accessory" muscles of inspiration, and indeed, in the hamster, the scalenes are silent during resting breathing and show inspiratory activity only when ventilation is increased by CO_2-enriched gas mixtures or when the mechanical load imposed on the inspiratory rib cage muscles is increased by elevated inspiratory airflow resistance or by phrenic nerve section (82). Also, both muscles in the dog are almost invariably silent during breathing (37, 180, 181), and so are the sternomastoids in humans (15, 31, 174). The scalenes in humans, however, are always active during inspiration (31, 38, 85, 174); they must, therefore, contribute to the inspiratory expansion of the rib cage and the lung.

Although the relative contributions of the scalenes and inspiratory intercostals to this expansion remain uncertain, studies in dogs have shown that the ΔP_{ao} values recorded during simultaneous contraction of the parasternal intercostals in one interspace and either the scalenes or the sternomastoids are nearly equal to the sum of the ΔP_{ao} values recorded during separate contraction (139). It appears, therefore, that the interaction between the inspiratory intercostals and the neck muscles on the lung is essentially additive. In addition, it is worth recalling that in seated humans breathing quietly, the sternum moves in the cranial direction during inspiration, such that the entire rib cage is displaced nearly along its relaxation trajectory (39). In contrast, in the dog, the scalenes are not active and the sternum moves in the caudal direction. This suggests that the inspiratory contraction of the scalenes in humans helps expand the rib cage with reduced distortion, and hence, with less elastic work.

B. Interaction Between the Inspiratory Intercostals and the Diaphragm

Coordinated contraction of the external and parasternal intercostals (together with the scalenes in humans) thus produces expansion of the lung by elevating the ribs and expanding the rib cage. If these muscles contract alone, however, the fall in pleural pressure is transmitted through the relaxed diaphragm to the abdominal cavity. As a result, abdominal pressure also falls, and the abdominal wall moves paradoxically inward. This pattern is typically observed both in animals (30, 46) and in humans (99, 131, 167) with diaphragmatic paralysis. Conversely, when the diaphragm contracts alone, such as in subjects with quadriplegia due to transection of the lower cervical cord, it produces a rise in abdominal pressure and causes a large expansion of the abdominal wall, but the fall in pleural pressure induces a paradoxical inward displacement of the rostral half of the rib cage (24, 76, 163, 196, 200). However, passive inflation induces simultaneous expansion of the rib cage and abdominal wall, and coordinated contraction of the inspiratory intercostals and the diaphragm during resting breathing in supine anesthetized dogs with all respiratory muscles intact (30, 46) and in seated healthy humans (39, 130, 149, 177) does the same. In fact, in these conditions, the chest wall displacement observed during a quiet inspiration is nearly superimposed on the relaxation trajectory. The conclusion can be drawn, therefore, that isolated contraction of either the inspiratory intercostals or the diaphragm causes substantial chest wall distortion, and that coordinated contraction of the two sets of muscles reduces the elastic work for a given lung expansion.

The interaction between the inspiratory intercostals and the diaphragm on the lung is more difficult to define. To examine this interaction, Di Marco et al. (64) induced, separately or simultaneously, electrical stimulation of the diaphragm in anesthetized dogs by applying trains of rectangular pulses to the phrenic nerves in the neck and electrical stimulation of the intercostal muscles by applying trains of similar pulses to the spinal cord through an electrode positioned in the epidural space. All phrenic nerve and intercostal stimulations were performed while the animal was apneic and the endotracheal tube was occluded. When the diaphragm and intercostal muscles were made to contract simultaneously at resting end-expiration, the ΔP_{ao} was found to be 17% greater than the sum of the ΔP_{ao} values produced by their separate contraction. The ratio between the ΔP_{ao} obtained during combined diaphragm-intercostal contraction and the sum of the ΔP_{ao} produced by their separate contraction was also found to vary as a function of lung volume; this ratio was 1.0 when transrespiratory pressure before muscle contraction was set at -10 cmH_2O, and it gradually increased to 1.9 when transrespiratory pressure before contraction was increased to $+30$ cmH_2O. Di Marco et al. (64) concluded, therefore, that the interaction between the diaphragm and the inspiratory intercostals on the lung is synergistic and that the degree of synergism increases with increasing lung volume. Furthermore, although the diaphragm and the parasternal intercostals shortened

markedly during both combined and isolated contraction, both muscles shortened less in the first instance than in the second. Consequently, the investigators further concluded that the synergism is largely related to the length-tension characteristics of the muscles; that is, by expanding the rib cage and causing pleural pressure to fall, the inspiratory intercostals prevent the active diaphragmatic muscle fibers from shortening excessively. Because the pressure-generating ability of these fibers closely depends on their length during contraction (104, 113, 159, 172, 179, 183), the diaphragm should therefore develop greater pressure than it does during isolated contraction. Contraction of the diaphragm might similarly impede the shortening of the inspiratory intercostals and allow them to develop greater force (64).

However, the use of an epidural electrode to activate the inspiratory intercostal muscles and to obtain a quantitative assessment of the diaphragm-intercostal interaction may not be optimal because this technique does not reproduce the gradients of external and parasternal intercostal activity observed during spontaneous breathing (see sect. III*A*). Instead, it elicits a forceful and uniform activation of the muscles over a large fraction of the rib cage. In addition, this technique induces strong contraction of all the expiratory muscles of the rib cage, including the triangularis sterni, as well as a number of muscles that, in the dog, are not involved in the act of breathing, such as the pectoralis, the serratii, the scalenes, and the sternomastoids.

The interaction between the canine diaphragm and inspiratory intercostal muscles, therefore, was reexamined using a more controlled technique (36). The phrenic nerves in each animal were sectioned in the neck to induce a complete paralysis of the diaphragm, and the animal was breathing spontaneously. Consequently, only the inspiratory intercostals were activated, and the normal topographic distribution of neural drive to these muscles was maintained. Also, the diaphragm in many animals was activated by applying rectangular pulses to the distal ends of the phrenic nerves, but in some animals the nerves were given ramp stimulation so as to reproduce more closely the pattern of diaphragmatic and inspiratory intercostal activation during breathing. Whether the phrenic nerves were given ramp or rectangular stimulation, the rise in abdominal pressure observed during simultaneous contraction of the diaphragm and inspiratory intercostals was much smaller than that observed during isolated diaphragmatic contraction. The diaphragm, therefore, was longer in the first instance than in the second and yet, with the endotracheal tube occluded at FRC, ΔP_{ao} during simultaneous diaphragm-intercostal contraction was nearly the same as the sum of the ΔP_{ao} generated by the two sets of muscles during separate contraction. This observation suggests that there is a mechanism which reduces or eliminates the beneficial effect of the intercostal muscles on the pressure-generating ability of the diaphragm; this mechanism is uncertain but might be related to the decrease in rib cage compliance that occurs when the diaphragm contracts alone against an occluded airway at FRC (36). And indeed, when the endotracheal tube was left open such that rib cage compliance was maintained constant, the increase in transpulmonary pressure during simultaneous diaphragm-intercostal contraction was 23% greater than the sum of the individual pressures. Moreover, although the pressure-volume curve of the lung has a sigmoid shape, such that at high lung volumes, large changes in pressure produce only small changes in volume, the increase in lung volume during simultaneous diaphragm-intercostal contraction was 9% greater than the sum of the increases in lung volume during separate contraction. These results therefore confirm, in agreement with Di Marco et al. (64), that the diaphragm and the inspiratory intercostals do act synergistically on the lung during breathing.

C. Interaction Between the Expiratory Intercostals and the Abdominal Muscles

The four abdominal muscles with significant respiratory function in quadrupeds and in humans make up the ventrolateral wall of the abdomen. The rectus abdominis is the most ventral of these muscles. It originates from the ventral aspect of the sternum and the fifth, sixth, and seventh costal cartilages, and it runs caudally along the whole length of the abdominal wall to insert into the pubis. The muscle is enclosed in a sheath formed by the aponeuroses of the three muscles situated laterally. The most superficial of these is the external oblique, which originates by fleshy digitations from the external surface of the lower eight ribs, well above the costal margin, and radiates caudally to insert on the iliac crest, the inguinal ligament, and the linea alba. The internal oblique lies deep to the external oblique. Its fibers arise from the iliac crest and inguinal ligament and diverge rostrally to insert on the costal margin and an aponeurosis contributing to the rectus sheath. Finally, deep to the internal oblique, lies the transversus abdominis, which arises from the inner surface of the lower six ribs, runs circumferentially around the abdominal visceral mass, and terminates ventrally in the rectus sheath.

These four muscles have important functions as flexors (rectus abdominis) and rotators (external oblique, internal oblique) of the trunk, but as respiratory muscles, their main action is to pull the abdominal wall inward and to increase abdominal pressure. In so doing, they induce a cranial displacement of the diaphragm into the thoracic cavity, which leads to a rise in pleural pressure and a

decrease in lung volume. And indeed, during expiratory efforts, the abdominal muscles act in concert with the internal interosseous intercostals and the triangularis sterni to cause simultaneous inward displacement of the rib cage and abdomen.

The separate and combined actions of the expiratory intercostal and abdominal muscles on the lung and chest wall were recently examined in rabbits by D'Angelo et al. (22). Because the internal interosseous intercostals and the triangularis sterni cannot be activated in all interspaces simultaneously, the action of these muscles was evaluated by applying an external pressure of 40–50 cmH_2O on the rib cage; the action of the abdominal muscles was assessed by both compression of the abdomen with a similar external pressure and electrical stimulation of the muscles. During isolated compression of the rib cage, the decrease in lung volume was ~75% of the expiratory reserve volume (ERV). Also, the rise in pleural pressure caused a caudal displacement of the diaphragm and a rise in abdominal pressure leading to an expansion of the abdomen; isolated, voluntary contraction of the triangularis sterni and internal intercostals in normal humans similarly results in a rise in abdominal pressure and an expansion of the abdomen (57). On the other hand, during isolated compression of the abdomen or maximal electrical stimulation of the abdominal muscles in rabbits, the rise in pleural and abdominal pressure caused an expansion of the rib cage and a decrease in lung volume corresponding to ~65% of ERV (22). It appears, therefore, that the expiratory intercostal and abdominal muscles interact on the chest wall in much the same way as the inspiratory intercostals and the diaphragm do; that is, isolated contraction of either set of expiratory muscles produces clear-cut distortion of the chest wall and increases the elastic work of breathing, and coordinated contraction of the two sets of muscles reduces distortion and work.

The observations reported by D'Angelo et al. (22) further indicate that the sum of the lung volume decreases caused by separate compression of the rib cage and abdomen is substantially greater than the decrease produced by their simultaneous compression (i.e., ERV), and this would suggest that the interaction between the two sets of expiratory muscles on the lung could be antagonistic. However, as D'Angelo et al. (22) suggested, the lung deflation produced by simultaneous rib cage and abdominal compression was probably limited by the mechanical properties of the lung, in particular the closure of airways. In fact, the lengths of the expiratory intercostal and abdominal muscles are interdependent. Isolated contraction of the internal interosseous intercostals and the triangularis sterni, by causing expansion of the abdomen, should induce lengthening of the abdominal muscles. Conversely, isolated contraction of the abdominal muscles causes expansion of the rib cage and should induce lengthening of the expiratory intercostals. The two sets of muscles, therefore, might have a synergistic interaction on the lung, but this hypothesis has yet to be tested.

VII. INFLUENCE OF LUNG VOLUME ON INTERCOSTAL MUSCLE ACTION

When lung volume in supine dogs, cats, and rabbits (113, 159, 172, 183) and in humans (24, 195) is passively increased from FRC to total lung capacity (TLC), the fall in pleural pressure induced by selective stimulation of the phrenic nerves decreases gradually and continuously; in fact, the lung expanding action of the diaphragm is almost abolished at TLC. This prompted Di Marco et al. (62) to examine the volume dependence of the lung expanding action of the parasternal and external intercostals in supine anesthetized dogs. In each animal, these investigators thus introduced a stimulating electrode in the epidural space, as described in section VI*B*, so as to produce strong activation of the muscles over a large fraction of the rib cage. The internal interosseous intercostals in many interspaces and the triangularis sterni were also strongly activated, but the superficial muscles of the rib cage in these animals were severed. All stimulations were performed while the animal was apneic and the endotracheal tube was occluded.

When the stimulation was delivered at FRC, the average ΔP_{ao} was -16 cmH_2O. However, when transrespiratory pressure before stimulation was set at -10 cmH_2O to decrease lung volume below FRC, ΔP_{ao} during stimulation amounted to -24 cmH_2O, i.e., it was increased by 50%. Conversely, when lung volume before stimulation was increased above FRC by a transrespiratory pressure of 15 cmH_2O, ΔP_{ao} was reduced to -9 cmH_2O, and when lung volume was increased further by a transrespiratory pressure of 30 cmH_2O, ΔP_{ao} was only -5 cmH_2O. The investigators subsequently repeated the procedure after the internal intercostal nerves in interspaces 1–6 were sectioned at the costochondral junctions to denervate the parasternal intercostals and the triangularis sterni. The stimulations, therefore, involved exclusively the interosseous intercostals and the levator costae. Although the values of ΔP_{ao} in this condition were smaller than the values before denervation, the influence of lung volume was identical with respect to both its direction and its magnitude (62).

This effect of hyperinflation on the pressure generation might have been the result of an increase in the effect of the expiratory intercostals. Indeed, when lung volume in dogs is passively increased from FRC to TLC, the internal interosseous intercostals in many interspaces and the triangularis sterni lengthen by substantial

amounts (Fig. 5*B*) (51, 55). Therefore, in accordance with the length-tension characteristics of the muscles, the force exerted by both muscles in response to a given stimulation increases. In a subsequent study, however, Ninane and Gorini (168) produced selective activation of the canine parasternal intercostals by electrical stimulation of the internal intercostal nerves at the costochondral junctions. The triangularis sterni in these animals was entirely sectioned and did not, therefore, confound the measurements. Yet, in agreement with the observations of Di Marco et al. (62), the ΔP_{ao} obtained during stimulation at a transrespiratory pressure of 15 cmH_2O was only ~50% of the value obtained during stimulation at FRC.

The adverse effect of hyperinflation on the pressure-generating ability of the diaphragm is known to be primarily related to the decrease in muscle length (11, 24, 86, 104, 113, 179, 195). By analogy, therefore, the volume dependence of the pressure-generating ability of the inspiratory intercostals was initially attributed to the decrease in intercostal muscle length (62). To be sure, both the external intercostals in the rostral interspaces and the parasternal intercostals shorten with lung inflation, as shown in Figure 5. However, whereas the canine or the human diaphragm shortens by 20–30% of its resting FRC length during passive inflation from FRC to TLC (11, 79, 104, 166, 205), the inspiratory intercostals shorten by 10% or less (29, 54, 55, 63). Furthermore, in supine dogs, the resting FRC length of the external intercostals in the rostral interspaces is close to L_o, but the resting FRC length of the parasternal intercostals is 10–15% longer than L_o (78). As these muscles shorten by ~10% during inflation from FRC to TLC, they should therefore move toward L_o, rather than away from it. As a result, their force-generating ability should remain unchanged or slightly increase, and indeed, studies by Decramer, Jiang, and colleagues (30, 109) have shown that the canine parasternal intercostals generate a similar or slightly greater force during stimulation near TLC than during stimulation at FRC. The detrimental effect of inflation on the capacity of these muscles to generate a fall in pleural pressure (168) must, therefore, be the result of another mechanism.

This mechanism was identified in a study of the effect of lung volume on the coupling between the ribs and the lung (49). The experimental protocol followed in this study was similar to that described in section II*C*. External forces were thus applied in the cranial direction to individual rib pairs in supine, paralyzed dogs with the endotracheal tube occluded; the forces were applied first at FRC, then after passive inflation to a transrespiratory pressure of 10 cmH_2O, and finally after passive inflation to a transrespiratory pressure of 20 cmH_2O. The results obtained for all the ribs at the three lung volumes are shown in Figure 9. For the 9th and 10th rib pairs, the ΔP_{ao} produced by a given force increased slightly with increasing lung volume, and this provides further support to the idea that the coupling between the ribs and the lung is primarily determined by the area of the lung subtended by the ribs (see sect. II*C*); that is, as lung volume is passively increased above FRC, the zone of apposition of the diaphragm to the rib cage decreases in size (154, 155), and the area of the lung subtended by the most caudal ribs increases. However, for all the ribs situated cranial to the zone of apposition (ribs 2–7), the ΔP_{ao} produced by a given force decreased markedly with increasing lung volume. Because the forces applied to the ribs were the same at all lung volumes, this decrease in ΔP_{ao} could not be attributed to the length-tension characteristics of the muscles. On the other hand, as the ribs rotate cranially with lung inflation, they become oriented more transversely relative to the sagittal midplane. Consequently, a given cranial rib displacement is associated with a smaller outward displacement, as shown in Figure 22. In fact, at 20 cmH_2O transrespiratory pressure, the cranial rib displacement produced by a given force was moderately reduced, but the outward rib displacement was nearly abolished. As pointed out in section V*C*, a given rib displacement in the outward direction in the dog produces a much greater increase in lung volume than the same rib displacement in the cranial direction (58). Thus the primary cause of the decrease in the respiratory effect of the inspiratory intercostal muscles at high lung volumes is the change in the orientation and motion of the ribs.

Although the effect of lung volume on the pressure-generating ability of the intercostal muscles in humans

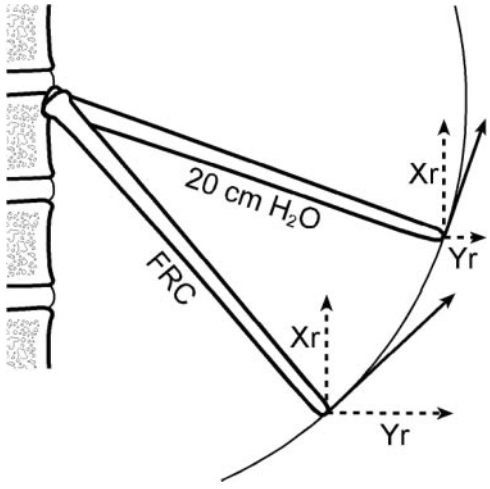

FIG. 22. Dorsal view of the spine and one rib in its position at FRC and its position at 20 cmH_2O transrespiratory pressure. Because the rib at FRC is slanted caudally, it moves both cranially (Xr) and outward (Yr) during cranial loading. However, at 20 cmH_2O transrespiratory pressure, the rib is almost horizontal. Therefore, loading the rib causes a cranial displacement with little or no outward displacement. [From De Troyer and Leduc (49).]

is uncertain, the bucket-handle rotation of the human ribs during passive inflation (209) is similar in magnitude to that observed in the dog (144). One would predict, therefore, that the coupling between the ribs and the lung in humans would also decrease with increasing lung volume.

VIII. WHY IS NEURAL DRIVE TO THE INTERCOSTAL MUSCLES MATCHED WITH MECHANICAL ADVANTAGE?

We emphasized in section III that the distributions of activity among both the external intercostals and the internal interosseous intercostals in the dog and in humans and among the parasternal intercostals in the dog match the distributions of mechanical advantage. Thus, in each of these muscle groups, neural drive during quiet breathing is greater in the areas with the greatest mechanical advantage than in the areas with a smaller mechanical advantage, and the muscles with mechanical advantages below some threshold remain electrically silent. As respiratory effort increases, activity increases in all areas, but the increase is greater in the areas with lower mechanical advantages than in the areas with higher mechanical advantages. A similar matching between neural drive and mechanical advantage has also been found in the canine costal diaphragm (110, 205), which leads to the question as to why the nervous system is "set" to produce a distribution of activity that mirrors the distribution of mechanical advantage. Statements have been made that such a matching may minimize the work of breathing (50, 110) or optimize in some way the performance of the respiratory muscle pump (134, 135), but the basis for such statements has been vague. In this section, we pursue this question by analyzing in a formal way the design of a mechanical system that is driven by active muscle forces.

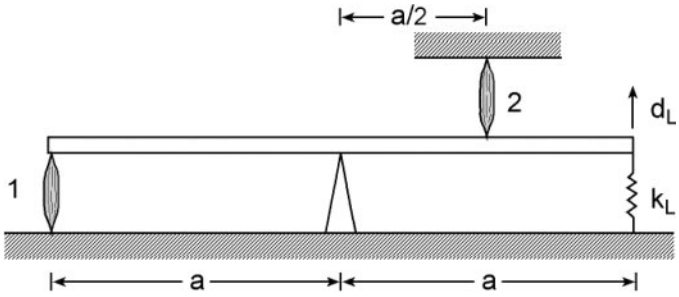

FIG. 23. Schematic model of a mechanical system that is driven by muscle forces. Identical muscles are attached to a lever at distances a to the left of the fulcrum (*muscle 1*) and $a/2$ to the right of the fulcrum (*muscle 2*). The load consists of a spring with spring constant k_L at the right end of the lever. Active forces in both muscles produce an upward displacement d_L of the end of the spring. For the system shown (*system A*), the fulcrum is rigid. For *system B*, the fulcrum is a spring with spring constant k_f.

A. The Mechanical System

The mechanical system is a simple lever, as shown in Figure 23. A load consisting of a spring with spring constant k_L is attached to the right end of the lever at a distance a from the fulcrum. The displacement of the end of the spring is denoted d_L. Two muscles are attached to the lever, one (*muscle 1*) at distance a to the left of the fulcrum, and a second (*muscle 2*) at distance $a/2$ to the right of the fulcrum. The two muscles are identical, and their function is to extend the spring. In the system pictured, the fulcrum is rigid (*system A*). The chest wall, however, contains many internal degrees of freedom and can be distorted, as pointed out in sections V and VI. Therefore, to simulate the chest wall better, we have also analyzed a system with an internal degree of freedom (*system B*); the fulcrum in this system is a spring with spring constant k_f, and its displacement is denoted d_f.

The mechanical advantage (μ) of a muscle is the ratio of the force delivered to the load to the force exerted by the muscle (see sect. IIA). For both *system A* and *system B*, the mechanical advantage of *muscle 1* (μ_1) is therefore twice that of *muscle 2* ($\mu_1 = 1$, $\mu_2 = 1/2$), and the relation between the displacement of the load and the forces F_1 and F_2 developed in the muscles is given by the following equation

$$k_L d_L = \mu_1 F_1 + \mu_2 F_2 \quad (2)$$

Parenthetically, it is worth pointing out that for both systems, if an external force is applied at the load to extend it (a procedure that would be analogous to a mechanical inflation of the passive chest wall), the lever rotates around the fulcrum, and the fractional shortening of *muscle 1* is twice that of *muscle 2*. This simple mechanical model is thus fully consistent with the analysis developed in section IIA.

Thus, using this model, we seek the values of F_1 and F_2 that accomplish a given task with minimum cost. As the role of the muscles is to extend the spring, a given task is described by a given value of d_L, and *Equation 2*, with a given value of d_L, constitutes a constraint governing the forces. In addition, because muscles generate tension, the forces must satisfy the following constraint

$$F_1 \geq 0, F_2 \geq 0 \quad (3)$$

Two cost functions are considered. Because it has been suggested that the observed distribution of intercostal muscle activity minimizes the work of breathing, the first cost function being considered is the work (W) done by the muscles. As Minetti and Alexander (158) have pointed out, however, the metabolic cost of muscle activation is a more sensible cost function than work. Metabolic energy expenditure, therefore, is taken as the second cost function.

B. Minimum Work

For *system A* (rigid fulcrum), the work done by the muscles is transmitted to the load and stored in the elastic energy of the extended spring. Therefore

$$W = \frac{1}{2} k_L d_L^2 \tag{4}$$

So for a given value of d_L, W is fixed, and the work done by the two muscles together is the same for any combination of F_1 and F_2 that satisfies *Equation 2*. In other words, for *system A*, the solution to the problem is not unique, and the distribution of activity among the two muscles is independent of the distribution of mechanical advantages.

For *system B* (elastic fulcrum), the work done by the muscles is stored in the elastic energies of both the load spring and the spring at the fulcrum. Consequently,

$$W = \frac{1}{2} k_L d_L^2 + \frac{1}{2} k_f d_f^2 \tag{5}$$

$$k_f d_f = 2F_1 - \frac{1}{2} F_2 \tag{6}$$

Because d_L is specified, the minimum work solution for this system is the solution for which $d_f = 0$, i.e., $F_2 = 4F_1$. The minimum work solution for *system B*, therefore, is the solution where the larger force is carried by the muscle with a smaller mechanical advantage, which is the opposite to the pattern of intercostal muscle activation during breathing. This analysis thus suggests that the distribution of forces that minimizes the work done by the muscles has no relation to the distribution of mechanical advantages.

C. Minimum Metabolic Cost

The metabolic cost of muscle contraction has not been determined as a function of all the variables of muscle action, such as the level of activity, the rate of shortening, and the time dependence of these variables, but data are available that provide a guide for a model of this cost function (211). A heat of activation is released when a muscle is activated whether the muscle is held at constant length or allowed to shorten. We assume that the metabolic cost of this heat of activation (C_{act}) is proportional to the level of activation and, hence, to the active force developed by the muscle. For maximally activated muscles, heat is also released if the muscle shortens, and for small amounts of shortening, the heat of shortening is proportional to the magnitude of shortening. We also assume that the heat of shortening is proportional to the level of activation and, hence, proportional to active force. Thus the heat of shortening is proportional to the work done by the muscle, and this cost can be combined with the cost of the work done into a single expression, denoted C_{work}, that is proportional to W. We assume that these are the dominant contributions to the metabolic cost of muscle activation, and we hypothesize the following cost function (C), where α and β are constants

$$C = C_{act} + C_{work}$$

$$C_{act} = \alpha(F_1 + F_2) \quad C_{work} = \beta W \tag{7}$$

It should be pointed out that Minetti and Alexander (158) made the same assumptions in their modeling of the metabolic cost of walking and running, and their cost function reduces to *Equation 7* in the limit of slow shortening.

Now we seek the values of F_1 and F_2 that minimize the cost function given by *Equation 7*, subject to the constraints given by *Equations 2* and *3*. For *system A*, the value of W is given once d_L is specified. Consequently, C_{work} is fixed, and C is minimized by the values of F_1 and F_2 that minimize C_{act} subject to the constraint equations. In addition, the value of F that delivers a given force to the load is smaller in the muscle with higher mechanical advantage. Therefore, C_{act} is minimized by setting the force in the muscle with a lower mechanical advantage at zero and setting the force in the muscle with the greatest mechanical advantage at the value that satisfies *Equation 2*. This solution, which is independent of the value of d_L, is closer to the pattern of intercostal muscle activity than was the previous one, but is still clearly different.

For *system B*, W is expressed in terms of F_1 and F_2 by substituting for d_f in *Equation 5* from *Equation 6*. An analysis of the problem of minimizing the resulting quadratic function of F_1 and F_2 subject to the constraints given by *Equations 2* and *3* yields the following solution

$$\text{For } d_L \le \frac{1}{6}(k_f/k_L)(\alpha/\beta)$$
$$F_1 = k_L d_L \qquad F_2 = 0 \tag{8}$$

$$\text{For } d_L \ge \frac{1}{6}(k_f/k_L)(\alpha/\beta)$$
$$F_1 = \frac{1}{3} k_L d_L + \frac{1}{9} k_f(\alpha/\beta) \quad F_2 = \frac{4}{3} k_L d_L - \frac{2}{9} k_f(\alpha/\beta) \tag{9}$$

The relationships between F_1 and F_2 and d_L for the particular case, $k_f/k_L = 6$, are shown in Figure 24*A*, and the corresponding relationships between C_{act} and C_{work} and d_L are shown in Figure 24, *B* and *C*, respectively. All values

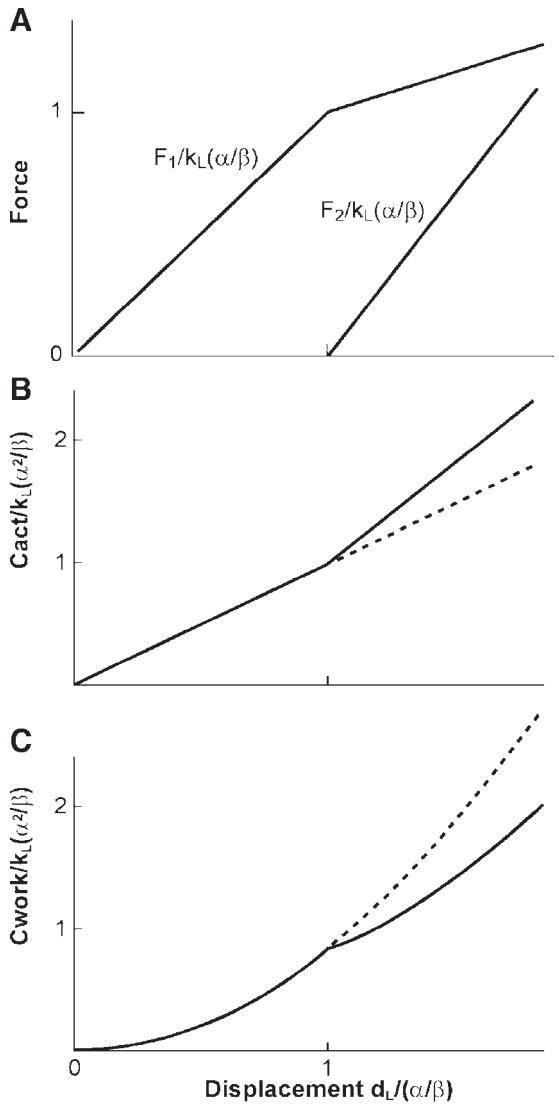

FIG. 24. *A*: relationships between the optimum forces in *muscles 1* (F_1) and *2* (F_2) and the displacement of the load(d_L) for *system B* for the particular case $k_f/k_L = 6$. The displacement is nondimensionalized by α/β, where α and β are the two constants in the cost function given by *Eq. 7*, and forces are nondimensionalized by $k_L(\alpha/\beta)$. *B* and *C*: relationships between the metabolic cost of the heat of activation (C_{act}) and $d_L/(\alpha/\beta)$ and between the metabolic cost of work (C_{work}) and $d_L/(\alpha/\beta)$, respectively. Metabolic costs are nondimensionalized by $k_L(\alpha^2/\beta)$. In the optimal solution (solid lines), for $d_L/(\alpha/\beta) < 1$, *muscle 1* is active and *muscle 2* is silent; for $d_L/(\alpha/\beta) > 1$, however, both muscles are active. For the optimal solution, C_{act} is larger and C_{work} is smaller than they would be if *muscle 2* remained silent for $d_L/(\alpha/\beta) > 1$ (dashed lines).

of k_f would yield qualitatively similar plots. For small values of d_L (*Eq. 8*), *muscle 1* is active and F_1 increases linearly with d_L, but *muscle 2* is silent ($F_2 = 0$). In this condition, C_{act}, which is a linear function of F, is larger than C_{work}, which is quadratic in F. In other words, for small values of d_L, C_{act} is the dominant term in the metabolic cost, and it is minimized by using only the muscle with the larger mechanical advantage. However, for values of d_L greater than the critical value, $d_L/(\alpha/\beta) = 1$ (*Eq. 9*), both muscles are active, and the forces in both increase linearly with increasing d_L. For these larger values of d_L, C_{work} becomes significant, and as *Eqs. 5* and *6* indicate, W and hence C_{work} are reduced by activation of *muscle 2*. Activation of this muscle causes an increase in C_{act}, but the decrease in C_{work} more than compensates for this increase. Thus the total cost C is minimized by a distribution of forces between the two muscles. The optimal design of the control system for this simple model, by and large, would thus be similar to the design of the control system for the intercostal muscles.

Arguments about the rationale for the design of biological systems have a weak foundation. In such arguments, simple objectives and simple costs are hypothesized, and other demands and constraints on the system are ignored. Also, any conclusion about the rationale for the design is necessarily speculative. Furthermore, because the detailed mechanical properties of the chest wall are complicated and largely unknown, the model analyzed in this section is highly schematic. Nonetheless, for what it is worth, this formal analysis provides a potential explanation for the matching between the distribution of activity among the intercostal muscles during breathing and the distribution of mechanical advantage; that is, muscles with a greater mechanical advantage would be preferentially activated because for a given lung expansion, the metabolic cost associated with the heat of activation is smaller for these muscles. Muscles with a smaller mechanical advantage would also be active when this activity reduces the total metabolic cost by reducing the distortion of the rib cage from its minimum energy configuration.

The results of this analysis can also provide a potential explanation for the fact that the matching between the amplitude of neural drive and the mechanical advantage applies to the different bundles within a particular muscle group (e.g., the external intercostals in the different interspaces) but does not apply across muscle groups. Two examples of such disproportionality may be considered. The first one concerns the scalenes and parasternal intercostals in the dog. As shown in Figure 4, the scalenes in this animal have the same mechanical advantage as the parasternal intercostal in the seventh interspace (54, 137), yet whereas the latter is active during inspiration, the former are electrically silent, including when inspiratory drive is increased by CO_2-enriched gas mixtures or elevated inspiratory aiflow resistance (37). The model in Figure 23 does not directly explain this observation. In this model, however, the two muscles are identical, whereas, in fact, the scalenes in the dog, in particular their medial head, are much longer than the parasternal intercostals. If one of the muscles in the model were longer, the cost of activation would be greater, and the critical displacement of the load at which this cost was balanced by a reduction in the cost of distortion would also be greater. The speculation might therefore be of-

fered that, in the dog, the scalenes remain silent at displacements at which shorter muscles with the same mechanical advantage are activated.

The second example of disproportionality concerns the parasternal intercostals versus the diaphragm. Although the mechanical advantage of the parasternal intercostals is considerably smaller than that of the diaphragm (205), muscle bundles in the parasternal intercostals may show maximal activation during inspiratory efforts (50, 134), but the diaphragm does not (9, 98). The optimum design specifies the forces that are exerted by the two muscles, and because the two muscles in the model are identical, the relation between force and level of activation is the same for both. However, if the two muscles had different cross-sectional areas, the level of activation per unit force would be smaller in the muscle with a greater cross-sectional area, and for the same force, the level of activation would also be smaller. Thus the optimum level of activation depends on muscle mass. If muscles have only a respiratory function, one might expect that the distribution of mass would be set in such a way that a maximal activation of all the muscles would correspond to a maximum respiratory effort. However, for muscles with various functions, the mass might be set for a different, nonrespiratory function. One cannot know all the functions of a muscle. However, it is known that the diaphragm participates in functions such as expulsive maneuvers and lifting, and its level of activation is greater during expulsive efforts than during inspiratory efforts (98). Thus its mass might be set at a value greater than the optimum for respiration. If so, it would produce an optimum force for respiration at submaximal levels of activation.

IX. SUMMARY AND CONCLUSIONS

The respiratory functions of the intercostal muscles have been controversial throughout medical history. The recent application to the respiratory system of the reciprocity theorem of Maxwell, however, has allowed the mechanical advantages of the muscles to be assessed. Both in the dog and in humans, the external intercostals in the dorsal portion of the rostral interspaces have a large inspiratory mechanical advantage, but this advantage decreases in the ventral and the caudal direction such that in the ventral portion of the caudal interspaces, it is reversed into an expiratory mechanical advantage. The internal interosseous intercostals in the caudal interspaces also have a large expiratory mechanical advantage, but this advantage decreases in the cranial direction and, for the rostral interspaces, in the ventral direction as well. The intercartilaginous portion of the internal intercostals (the so-called parasternal intercostals), therefore,

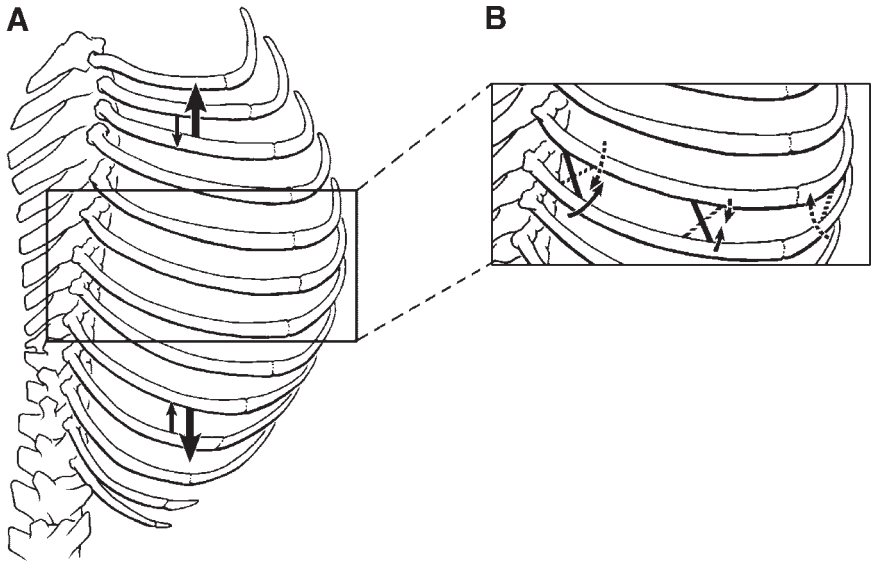

FIG. 25. Diagram illustrating the two mechanisms responsible for the distribution of mechanical advantage of the intercostal muscles. The first mechanism (*A*) depends on the nonuniform coupling between the ribs and the lung and the consequent difference between the effects of equal and opposite forces on adjacent ribs (arrows). In a rostral interspace, the fall in P_{ao} produced by the cranial displacement of a particular rib is larger than the rise in P_{ao} caused by the caudal displacement of the rib above, whereas in a caudal interspace, the fall in P_{ao} produced by the cranial displacement of a particular rib is smaller than the rise in P_{ao} caused by the caudal displacement of the rib above. Consequently, the external and internal intercostals in the rostral interspaces have an inspiratory bias, whereas those in the caudal interspaces have an expiratory bias. The second mechanism, illustrated for a rather rostral interspace in *B*, is the result of the difference between the magnitudes of the moments applied by the muscles to the upper and lower ribs of the interspace (arrows). In the dorsal part of the interspace, this difference confers to the external intercostal muscle an inspiratory mechanical advantage and to the internal intercostal an expiratory mechanical advantage. However, because of the curvature of the ribs, the respective inspiratory and expiratory mechanical advantages of the two muscles decrease in the ventral direction, and in the vicinity of the sternum, the internal (parasternal) intercostal has an inspiratory mechanical advantage.

have a large inspiratory mechanical advantage, whereas the triangularis sterni has a large expiratory mechanical advantage. This distribution of mechanical advantage is the result of two mechanisms, as illustrated in the diagram shown in Figure 25. The first mechanism (Fig. 25*A*) depends on the nonuniform coupling between rib displacement and lung expansion; it has larger effects in the ventral region of the rib cage than in the dorsal region and accounts for the rostrocaudal gradients in mechanical advantage. The second mechanism (Fig. 25*B*) is the conventional Hamberger mechanism, adjusted to account for the three-dimensional configuration of the rib cage. Its magnitude is larger in the dorsal region of the rib cage than in the ventral region, and its sign is reversed in the vicinity of the costochondral junctions. It thus accounts for the differences between the interosseous and intercartilaginous portions of the internal intercostals and between the external intercostals and the triangularis sterni.

The topographic distribution of mechanical advantage implies that the functions of the muscles during breathing depend on the topographic distribution of neural drive. The external intercostals and the parasternal intercostals are active only during the inspiratory phase of the breathing cycle. External intercostal activity, however, is greatest in the dorsal portion of the rostral interspaces, and it decreases both ventrally and caudally such that the muscles in the caudal interspaces remain silent. As a result, the external intercostals and parasternal intercostals have an inspiratory function during breathing, and coordinated activity between them elevates the ribs along their relaxation trajectory and contributes to the lung expansion. These two sets of muscles also reduce the shortening of the diaphragm during inspiration and thereby enhance its pressure-generating ability. In contrast, the internal interosseous intercostals and the triangularis sterni are active only during the expiratory phase of the breathing cycle, and internal intercostal activity is greatest in the caudal, rather than rostral, interspaces. These two muscles, therefore, have an expiratory function during breathing, and they act in concert with the abdominal muscles to deflate the chest wall and the lung.

The external intercostals and the internal interosseous intercostals thus have opposite actions on the lung during breathing. These opposite actions, however, are largely the result of selective regional activation of the muscles, rather than the different orientations of the muscle fibers, as has been conventionally thought. One of the most intriguing aspects of intercostal muscle function is, in fact, the remarkable congruence between the topographic distribution of neural drive to the muscles and the topographic distribution of mechanical advantage. The mechanisms that establish this relationship are uncertain, but a critical evaluation of the successive steps in the activation process suggests that central nervous factors, either spinal or supraspinal, play a predominant role. The beneficial effects of this relationship are also unknown. However, the analysis of a simple mechanical system indicates that such a matching between activation and mechanical advantage could reduce the total metabolic cost of breathing. It would therefore be tempting to speculate that activation and mechanical advantage might also be correlated in other systems. Such a correlation has recently been observed in the canine diaphragm (110), but the hypothesis remains to be tested in nonrespiratory systems.

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